

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

Requested Patent: EP0860433A1

Title:

QUINOLINE DERIVATIVES AND QUINAZOLINE DERIVATIVES INHIBITING
AUTOPHOSPHORYLATION OF GROWTH FACTOR RECEPTOR ORIGINATING IN
PLATELET AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME ;

Abstracted Patent: EP0860433 ;

Publication Date: 1998-08-26 ;

Inventor(s):

KOBAYASHI YOSHIKO (JP); SHIMIZU TOSHIYUKI (JP); KATO SHINICHIRO (JP);
MUROOKA HIDEKO (JP); OHYAMA SHINICHI (JP); KUBO KAZUO IYAKU (JP);
NISHITOBA TSUYOSHI (JP) ;

Applicant(s): KIRIN BREWERY (JP) ;

Application Number: EP19960935541 19961105 ;

Priority Number(s):

WO1996JP03229 19961105; JP19950313555 19951107; JP19960062121
19960223 ;

IPC Classification:

C07D215/20; C07D215/22; C07D215/36; C07D239/74; C07D239/88;
C07D239/93; C07D401/12; C07D405/12; C07D409/12; C07D491/056;
A61K31/47 ;

Equivalents: AU7340096, US6143764, WO9717329

ABSTRACT:

The present invention relates to novel quinoline derivatives and quinazoline derivatives represented by the following formula (I): A wherein R1 and R2 are each independently H or C1-C4-alkyl, or R1 and R2 together form C1-C3-alkylene, X is O, S or CH₂, W is CH or N, and Q is a substituted aryl group or substituted heteroaryl group B and their pharmaceutically acceptable salts, having platelet-derived growth factor receptor autophosphorylation inhibitory activity, to pharmaceutical compositions containing these compounds, and to methods for the treatment of diseases associated with abnormal cell growth such as tumors.

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets

(11)



EP 0 860 433 A1

(12)

EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:

26.08.1998 Bulletin 1998/35

(51) Int. Cl.⁶: C07D 215/20, C07D 215/22,

C07D 215/36, C07D 239/74,

C07D 239/88, C07D 239/93,

C07D 401/12, C07D 405/12,

C07D 409/12, C07D 491/056,

A61K 31/47

(21) Application number: 96935541.1

(22) Date of filing: 05.11.1996

(86) International application number:

PCT/JP96/03229

(87) International publication number:

WO 97/17329 (15.05.1997 Gazette 1997/21)

(84) Designated Contracting States:

CH DE FR GB LI

(30) Priority: 07.11.1995 JP 313555/95

23.02.1996 JP 62121/96

(71) Applicant:

KIRIN BEER KABUSHIKI KAISHA
Chuo-Ku, Tokyo 104 (JP)

(72) Inventors:

- KUBO, Kazuo,
Iyaku Tansaku Kenkyusho
Takasaki-shi, Gunma 370-12 (JP)
- OHYAMA, Shinichi,
Iyaku Tansaku Kenkyusho
Takasaki-shi, Gunma 370-12 (JP)
- SHIMIZU, Toshiyuki,
Iyaku Tansaku Kenkyusho
Takasaki-shi, Gunma 370-12 (JP)

• NISHITOBA, Tsuyoshi,
Iyaku Tansaku Kenkyusho
Takasaki-shi, Gunma 370-12 (JP)

• KATO, Shinichiro,
Iyaku Tansaku Kenkyusho
Takasaki-shi, Gunma 370-12 (JP)

• MUROOKA, Hideko,
Iyaku Tansaku Kenkyusho
Takasaki-shi, Gunma 370-12 (JP)

• KOBAYASHI, Yoshiko,
Iyaku Tansaku Kenkyusho
Takasaki-shi, Gunma 370-12 (JP)

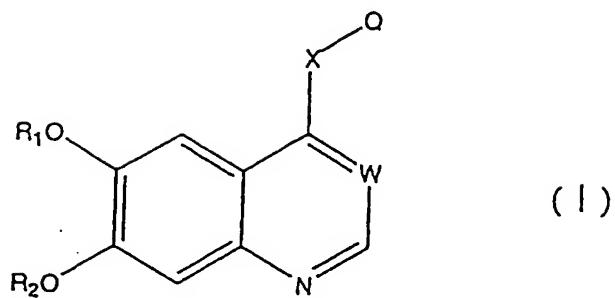
(74) Representative:

Kolb, Helga, Dr. Dipl.-Chem. et al
Hoffmann Eitle,
Patent- und Rechtsanwälte,
Arabellastrasse 4
81925 München (DE)

(54) **QUINOLINE DERIVATIVES AND QUINAZOLINE DERIVATIVES INHIBITING
AUTOPHOSPHORYLATION OF GROWTH FACTOR RECEPTOR ORIGINATING IN PLATELET
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME**

(57) The present invention relates to novel quinoline derivatives and quinazoline derivatives represented by the following formula (I):

EP 0 860 433 A1



[wherein R₁ and R₂ are each independently H or C₁-C₄-alkyl, or R₁ and R₂ together form C₁-C₃-alkylene, X is O, S or CH₂, W is CH or N, and Q is a substituted aryl group or substituted heteroaryl group] and their pharmaceutically acceptable salts, having platelet-derived growth factor receptor autophosphorylation inhibitory activity, to pharmaceutical compositions containing these compounds, and to methods for the treatment of diseases associated with abnormal cell growth such as tumors.

Description**FIELD OF THE INVENTION**

5 The present invention relates to novel quinoline derivatives and quinazoline derivatives having an inhibitory action against abnormal cell growth and to their pharmaceutically acceptable salts. More specifically, the present invention relates to novel quinoline derivatives and quinazoline derivatives having an inhibitory action against autophosphorylation of the platelet-derived growth factor receptor and to their pharmaceutically acceptable salts.

10 BACKGROUND OF THE INVENTION

Growth factors such as insulin, the epidermal growth factor and the platelet-derived growth factor (hereinafter referred to as PDGF) have an important role in cell growth. In particular, PDGF is known to be a powerful cell growth factor related to the control of cell growth and division (Cell 46, 155 (1986)). However, in diseases or pathophysiological 15 situations such as leukemia, cancers, psoriasis, glomerular nephritis, organofibrosis, atherosclerosis, restenosis after percutaneous coronary angioplasty or bypass surgery and rheumatoid arthritis, abnormal production of PDGF or PDGF receptor occurs at the pathophysiological sites, and abnormal cell growth is observed at the pathophysiological sites in such diseases. Namely, this is an excess of cell growth signals associated with overproduction of the PDGF or PDGF receptors. Thus, it is necessary to suppress cell growth signal transduction to improve these pathophysiological situations.

20 In one trial, it was reported that abnormal cell growth in pathophysiological situations was suppressed by administration of an anti-PDGF antibody (J. Exp. Med. 175, 1413 (1992)); however, there are problems such as *in vivo* stability and methods of administration as a therapeutic agent because the anti-PDGF antibody is a protein molecule.

On the other hand, in cells, PDGF is known to bind to the PDGF receptor to activate tyrosine kinase present in this 25 receptor. This receptor tyrosine kinase relates to intracellular signal transduction via autophosphorylation of the receptor itself and plays an important role in cell growth. In pathophysiological situations, this intracellular signal transduction is considered to be excessive. Therefore, inhibition of PDGF receptor autophosphorylation can be considered as another possible strategy to suppress cell growth signal transduction.

30 Examples of suppressing cell growth using the PDGF receptor autophosphorylation inhibitors, which are low molecular weight compounds, are described in the literature (Cancer Research 54, 6106 (1994); Proc. Natl. Acad. Sci. USA. 92, 2558 (1995)). Therefore, PDGF receptor autophosphorylation inhibitors could be useful in many diseases such as leukemia, cancers, psoriasis, glomerular nephritis, organofibrosis, atherosclerosis, restenosis after percutaneous coronary angioplasty or bypass surgery and rheumatoid arthritis.

35 Examples of previously known PDGF receptor autophosphorylation inhibitors include 3-arylquinolines (J. Med. Chem. 37, 2627 (1994); J. Med. Chem. 37, 2129 (1994) and Publication of Japanese Patent Laid-open No. 94/507643), 3-aryliquinoxalines (Cancer Research 54, 6106 (1994)), and 4-pyridyl-2-arylpurimidines (Proc. Natl. Acad. Sci. USA. 92, 2558 (1995)).

40 However, as far as the present inventors know, compounds which have a structure in which an aryl group or heteroaryl group is bonded to position 4 of the quinoline backbone or quinazoline backbone via one oxygen atom, sulfur atom or carbon atom and which have a PDGF receptor autophosphorylation inhibitory activity are not known.

45 Furthermore, as to previously known quinoline derivatives, {4-[(7-chloro-4-quinolonyloxy)phenyl](4-fluorophenyl)methanone is described in Publication of Examined Japanese Patent Application No. 89/246263. This known compound is used as a fungicide, and there are no reports as to its PDGF receptor autophosphorylation inhibitory activity.

Furthermore, 4-arylquinoline derivatives are described in J. Med. Chem. 14, 1060 (1971), Acta Chim. Hung. 112, 241 (1983), Publication of Examined Japanese Patent Application No. 88/51375, German Patent No. 3101544, Publication of Examined Japanese Patent Application No. 89/246263, and US Patent No. 3936461. These known compounds are each reported as an antihypertensive agent or intermediate for its production, agent to prevent harmful organisms (preservative), plant growth control agent, fungicide or anti-angina agent, respectively, and there are no reports as to their PDGF receptor autophosphorylation inhibitory activity.

50 Consequently, the development of novel compounds having the PDGF receptor autophosphorylation inhibitory activity would be of great industrial benefit.

A major objective of the present invention is to provide novel compounds having the PDGF receptor autophosphorylation inhibitory activity.

55 DISCLOSURE OF THE INVENTION

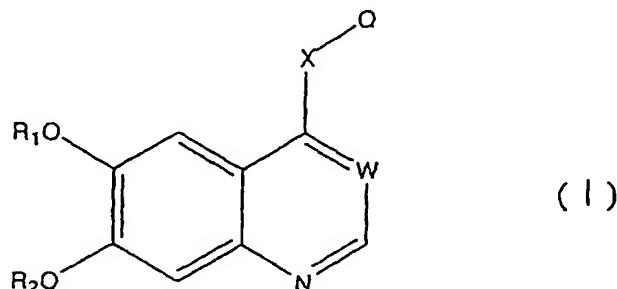
As a result of intensive studies to attain the abovementioned objective, the present inventors found that compounds having a structure in which an aryl group or heteroaryl group is bound to position 4 of the quinoline backbone or quin-

zoline backbone via one oxygen atom, sulfur atom or carbon atom best serve the objective, and thus came to complete the present invention based on this finding.

Namely, the present invention is to provide quinoline derivatives and quinazoline derivatives represented by the following formula (I), and pharmaceutically acceptable salts thereof:

5

10



15

{wherein R₁ and R₂ are each independently H, C₁-C₅-alkyl, or R₁ and R₂ together form C₁-C₃-alkylene, and W is CH or N,

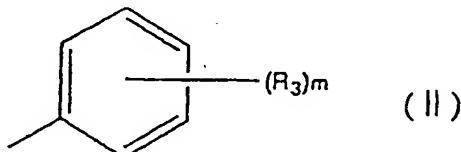
20

1. when W is CH,

25

(a) X is O or S, and Q is a phenyl group represented by formula (II):

30

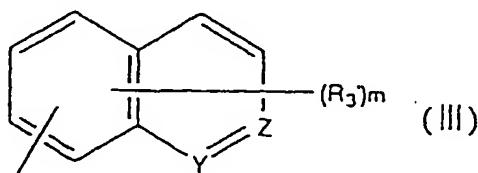


35

[wherein m is 1, 2 or 3, R₃ is each independently CN, OH, halogen, C₁-C₅-alkyl, C₁-C₄-alkoxy or C₂-C₄-acyl].

35

40



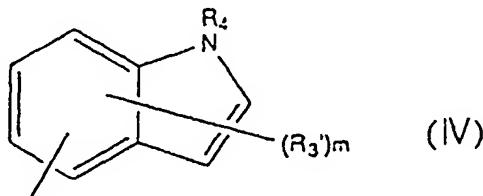
45

[wherein m is as defined as described above, R₃' is each independently OH, C₁-C₅-alkyl, C₁-C₄-alkoxy, and Y and Z are both or each independently N or CH],

or a group represented by formula (IV):

50

55



[wherein m and R₃' are as defined as described above, and R₄ is H, C₁-C₅-alkyl or C₂-C₄-acyl], and

(b) X is O, S or CH₂, and Q is a group represented by formula (V):

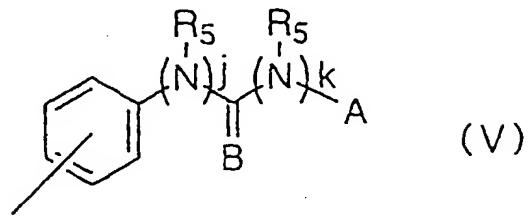
5

10

15

20

25



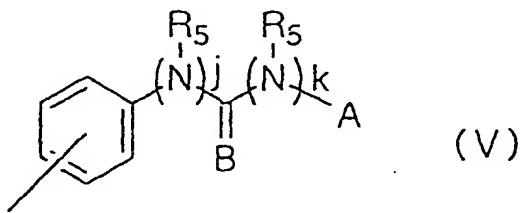
[wherein j and k are each independently 0 or 1, R₅ is each independently H or C₁-C₈-alkyl, C₁-C₅-alkenyl, cyclic (C₃-C₁₀) alkyl, C₁-C₄-alkoxycarbonyl, phenyl, naphthyl, furyl, thiienyl, benzoyl, substituted benzoyl, C₂-C₄-acyl, or 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaryl group having 1 or 2 nitrogen atoms and optionally having another hetero atom selected from the group consisting of nitrogen, oxygen and sulfur atoms, these alkyl group, aryl group and heteroaryl group represented by A may have 1 to 5 substituting groups selected from the group consisting of CN, NO₂, OH, NH₂, halogen, C₁-C₅-alkyl, cyclic (C₃-C₁₀) alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxycarbonyl, C₁-C₅-acyl, C₁-C₅-acyloxy, C₁-C₃-alkylenedioxy, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, CO₂H, CONH₂, N-(C₁-C₄-alkyl)amido, N,N-di-(C₁-C₄-alkyl)amido, C₂-C₄-alkylamido, trifluoromethyl, C₁-C₄-alkylthio, phenyl, substituted phenyl, phenoxy, substituted phenoxy, phenythio, substituted phenythio, phenyl(C₁-C₄-alkyl), substituted phenyl(C₁-C₄-alkyl); pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopyperazinyl, morpholinyl, quinolyl, quinazolinyl, benzoyl, substituted benzoyl and C₂-C₄-acyl, and B is O, S, NH, NCN, NR₆ or NOR₆ (wherein R₆ is C₁-C₅-alkyl).]

26

2. when W is N, X is O, S or CH₂, and Q is represented by formula (V):

30

35



40

BEST MODE FOR CARRYING OUT THE INVENTION

1. Compounds of the present invention

45 Compounds of the present invention are represented by the abovementioned formula (I), wherein R₁, R₂, W, X, Q, R₃, R₃', R₄, R₅, R₆, Y, Z, A', B, m, j and k are defined as described above.
Examples of specific substituents applicable in the present specification are as follows:

50 Halogen: chloro, bromo, fluoro, iodo;
C₁-C₅-alkyl: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, isopentyl, neopentyl, t-pentyl;
cyclic (C₃-C₁₀) alkyl: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl;
C₁-C₄-alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, s-butoxycarbonyl, t-butoxycarbonyl;
55 C₁-C₃-alkylenedioxy: methylenedioxy, ethylenedioxy, propylenedioxy;
C₁-C₄-alkoxy: methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy, t-butoxy;
C₂-C₄-acyl: acetyl, propionyl, butylyl;
C₁-C₄-alkylamino: methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, s-

butylamino, t-butylamino;

di-(C₁-C₄-alkyl) amino: dimethylamino, diethylamino, dipropylamino, dibutylamino;

C₂-C₄-alkylamido: acetamido, propionamido, butylamido;

C₁-C₄-alkylthio: methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, s-butylthio, t-butylthio;

5 substituted phenyl: a phenyl group substituted by 1 to 3 groups selected from the group consisting of CN, NO₂, OH, NH₂, halogen, C₁-C₄-alkyl, cyclic (C₃-C₁₀)alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxycarbonyl, C₁-C₃-alkylenedioxy, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, C₂-C₄-alkylamido, trifluoromethyl, C₁-C₄-alkylthio, phenyl, phenoxy, phenylthio, phenyl(C₁-C₄-alkyl), benzoyl and C₂-C₄-acyl;

10 substituted phenoxy: a phenoxy group substituted by 1 to 3 groups selected from the group consisting of CN, NO₂, OH, NH₂, halogen, C₁-C₄-alkyl, cyclic (C₃-C₁₀)alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxycarbonyl, C₁-C₃-alkylenedioxy, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, C₂-C₄-alkylamido, trifluoromethyl, C₁-C₄-alkylthio, phenyl, phenoxy, phenylthio, phenyl(C₁-C₄-alkyl), benzoyl and C₂-C₄-acyl;

15 substituted phenylthio: a phenylthio group substituted by 1 to 3 groups selected from the group consisting of CN, NO₂, OH, NH₂, halogens, C₁-C₄-alkyl, cyclic (C₃-C₁₀)alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxycarbonyl, C₁-C₃-alkylenedioxy, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, C₂-C₄-alkylamido, trifluoromethyl, C₁-C₄-alkylthio, phenyl, phenoxy, phenylthio, phenyl(C₁-C₄-alkyl), benzoyl and C₂-C₄-acyl;

20 substituted benzoyl: a benzoyl group substituted by 1 to 3 groups selected from the group consisting of CN, NO₂, OH, NH₂, halogens, C₁-C₄-alkyl, cyclic (C₃-C₁₀)alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxycarbonyl, C₁-C₃-alkylenedioxy, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, C₂-C₄-alkylamido, trifluoromethyl, C₁-C₄-alkylthio, phenyl, phenoxy, phenylthio, phenyl(C₁-C₄-alkyl), benzoyl and C₂-C₄-acyl.

The compounds represented by formula (I) may be acid addition salts and base addition salts thereof. The compounds of the present invention include these addition salts. Further, the compounds of the present invention, including these addition salts, include hydrates thereof.

25 Examples of the acid addition salts include salts with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and nitric acid, and salts with organic acid such as maleic acid, fumaric acid, malic acid, oxalic acid, tartaric acid, succinic acid, citric acid, acetic acid, lactic acid, methanesulfonic acid and p-toluenesulfonic acid.

30 Further, examples of the base addition salts include salts with alkaline metal compounds (e.g., sodium hydroxide and potassium hydroxide), salts with alkaline earth metal compounds (e.g., calcium hydroxide and magnesium hydroxide), ammonium salts and salts with organic bases (e.g., triethylamine, ethanolamine).

Further, when these addition salts are used as drugs, the acids and bases naturally have to be pharmaceutically acceptable.

35 Representative examples of the compounds of formula (I) of the present invention are shown in Table 1. They are preferred embodiments of compound groups.

40

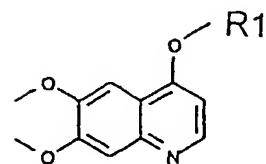
45

50

55

TABLE 1

5



10

15

Compound No.	R1	Compound No.	R1
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

40

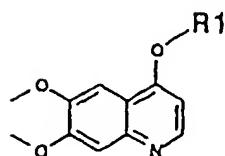
45

50

55

TABLE 1 (continued)

5



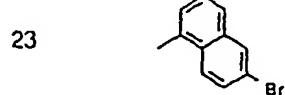
10

Compound No.	R1	Compound No.	R1
--------------	----	--------------	----

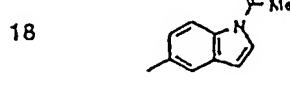
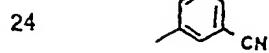
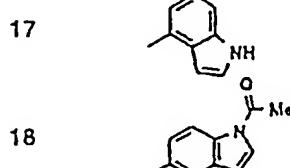
15



20



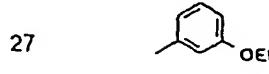
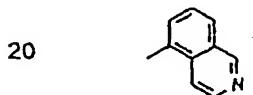
25



30



35



40



45

50

55

TABLE 1 (continued)

5



10

	Compound No.	R2	Compound No.	R2
15	29		36	
20	30		37	
25	31		38	
30	32		39	
35	33		40	
40	34		41	
45	35		42	

50

55

TABLE 1 (continued)

5



10

Compound No.	R2	Compound No.	R2
155		159	
156		160	
157		161	
158		162	

40

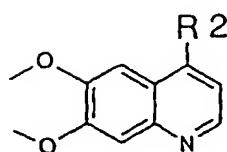
45

50

55

TABLE 1 (continued)

5



10

	Compound No.	R2	Compound No.	R2
15	176		182	
20	177		183	
25	178		184	
30	179		185	
35	180		186	
40	181		187	

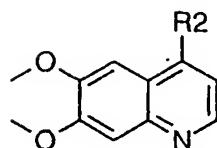
45

50

55

TABLE 1 (continued)

5



10

	Compound No.	R2	Compound No.	R2
15	284		288	
20	285		289	
25	286		290	
30	287			
35				
40				

45

50

55

TABLE 1 (continued)

5

10

15

20

25

30

35

40

45

50

55

60

65

70

75

80

85

90

95

100

105

110

115

120

125

130

135

140

145

150

155

160

165

170

175

180

185

190

195

200

205

210

215

220

225

230

235

240

245

250

255

260

265

270

275

280

285

290

295

300

305

310

315

320

325

330

335

340

345

350

355

360

365

370

375

380

385

390

395

400

405

410

415

420

425

430

435

440

445

450

455

460

465

470

475

480

485

490

495

500

505

510

515

520

525

530

535

540

545

550

555

560

565

570

575

580

585

590

595

600

605

610

615

620

625

630

635

640

645

650

655

660

665

670

675

680

685

690

695

700

705

710

715

720

725

730

735

740

745

750

755

760

765

770

775

780

785

790

795

800

805

810

815

820

825

830

835

840

845

850

855

860

865

870

875

880

885

890

895

900

905

910

915

920

925

930

935

940

945

950

955

960

965

970

975

980

985

990

995

1000

1005

1010

1015

1020

1025

1030

1035

1040

1045

1050

1055

1060

1065

1070

1075

1080

1085

1090

1095

1100

1105

1110

1115

1120

1125

1130

1135

1140

1145

1150

1155

1160

1165

1170

1175

1180

1185

1190

1195

1200

1205

1210

1215

1220

1225

1230

1235

1240

1245

1250

1255

1260

1265

1270

1275

1280

1285

1290

1295

1300

1305

1310

1315

1320

1325

1330

1335

1340

1345

1350

1355

1360

1365

1370

1375

1380

1385

1390

1395

1400

1405

1410

1415

1420

1425

1430

1435

1440

1445

1450

1455

1460

1465

1470

1475

1480

1485

1490

1495

1500

1505

1510

1515

1520

1525

1530

1535

1540

1545

1550

1555

1560

1565

1570

1575

1580

1585

1590

1595

1600

1605

1610

1615

1620

1625

1630

1635

1640

1645

1650

1655

1660

1665

1670

1675

1680

1685

1690

1695

1700

1705

1710

1715

1720

1725

1730

1735

1740

1745

1750

1755

1760

1765

1770

1775

1780

1785

1790

1795

1800

1805

1810

1815

1820

1825

1830

1835

1840

1845

1850

1855

1860

1865

1870

1875

1880

1885

1890

1895

1900

1905

1910

1915

1920

1925

1930

1935

1940

1945

1950

1955

1960

1965

1970

1975

1980

1985

1990

1995

2000

2005

2010

2015

2020

2025

2030

2035

2040

2045

2050

2055

2060

2065

2070

2075

2080

2085

2090

2095

2100

2105

2110

2115

2120

2125

2130

2135

2140

2145

2150

2155

2160

2165

2170

2175

2180

2185

2190

2195

2200

2205

2210

2215

2220

2225

2230

2235

2240

2245

2250

2255

2260

2265

2270

2275

2280

2285

2290

2295

2300

2305

2310

2315

2320

2325

2330

2335

2340

2345

2350

2355

2360

2365

2370

2375

2380

2385

2390

2395

2400

2405

2410

2415

2420

2425

2430

2435

2440

2445

2450

2455

2460

2465

2470

2475

2480

2485

2490

2495

2500

2505

2510

2515

2520

2525

2530

2535

2540

2545

2550

2555

2560

2565

2570

2575

2580

2585

2590

2595

2600

2605

2610

2615

2620

2625

2630

2635

2640

2645

2650

2655

2660

2665

2670

2675

2680

2685

2690

2695

2700

2705

2710

2715

2720

2725

2730

2735

2740

2745

2750

2755

2760

2765

2770

2775

2780

2785

2790

2795

2800

2805

2810

2815

2820

2825

2830

2835

2840

2845

2850

2855

2860

2865

2870

2875

2880

2885

2890

2895

2900

2905

2910

2915

2920

2925

2930

2935

2940

2945

2950

2955

2960

2965

2970

2975

2980

2985

2990

2995

3000

3005

3010

3015

3020

3025

3030

3035

3040

3045

3050

3055

3060

3065

3070

3075

3080

3085

3090

3095

3100

3105

3110

3115

3120

3125

3130

3135

3140

3145

3150

3155

3160

3165

3170

3175

3180

3185

3190

3195

3200

3205

3210

3215

3220

3225

3230

3235

3240

3245

3250

3255

3260

3265

3270

3275

3280

3285

3290

3295

3300

3305

3310

3315

3320

3325

3330

3335

3340

3345

3350

3355

3360

3365

3370

3375

3380

3385

3390

3395

3400

3405

3410

3415

3420

3425

3430

3435

3440

3445

3450

3455

3460

3465

3470

3475

3480

3485

3490

3495

3500

3505

3510

3515

3520

3525

3530

3535

3540

3545

3550

3555

3560

3565

3570

3575

3580

3585

3590

3595

3600

3605

3610

3615

3620

3625

3630

3635

3640

3645

3650

3655

3660

3665

3670

3675

3680

3685

3690

3695

3700

3705

3710

3715

3720

3725

3730

3735

3740

3745

3750

3755

3760

3765

3770

3775

3780

3785

3790

3795

3800

3805

3810

3815

3820

3825

3830

3835

3840

3845

3850

3855

3860

3865

3870

3875

3880

3885

3890

3895

3900

3905

3910

3915

3920

3925

3930

3935

3940

3945

3950

3955

3960

3965

3970

3975

3980

3985

3990

3995

4000

4005

4010

4015

4020

4025

4030

4035

4040

4045

4050

4055

4060

4065

4070

4075

4080

4085

4090

4095

4100

4105

4110

4115

4120

4125

4130

4135

4140

4145

4150

4155

4160

4165

4170

4175

4180

4185

4190

4195

4200

4205

4210

4215

4220

4225

4230

4235

4240

4245

4250

4255

4260

4265

4270

4275

4280

4285

4290

4295

4300

4305

4310

4315

4320

4325

4330

4335

4340

4345

4350

4355

4360

4365

4370

4375

4380

4385

4390

4395

4400

4405

4410

4415

4420

4425

4430

4435

4440

4445

4450

4455

4460

4465

4470

4475

4480

4485

4490

4495

4500

4505

4510

4515

4520

4525

4530

4535

4540

4545

4550

4555

4560

4565

4570

4575

4580

4585

4590

4595

4600

4605

4610

4615

4620

4625

4630

4635

4640

4645

4650

4655

4660

4665

4670

4675

4680

4685

4690

4695

4700

4705

4710

4715

4720

4725

4730

4735

4740

4745

4750

4755

4760

4765

4770

4775

4780

4785

4790

4795

4800

4805

4810

4815

4820

4825

4830

4835

4840

4845

4850

4855

4860

4865

4870

4875

4880

4885

4890

4895

4900

4905

4910

4915

4920

4925

4930

4935

4940

4945

4950

4955

4960

4965

4970

4975

4980

4985

4990

4995

5000

5005

5010

5015

5020

5025

5030

5035

5040

5045

5050

5055

5060

5065

5070

5075

5080

5085

5090

5095

5100

5105

5110

5115

5120

5125

5130

5135

5140

5145

5150

5155

5160

5165

5170

5175

5180

5185

5190

5195

5200

5205

5210

5215

5220

5225

5230

5235

5240

5245

5250

5255

5260

5265

5270

5275

5280

5285

5290

5295

5300

5305

5310

5315

5320

5325

5330

5335

5340

5345

5350

5355

5360

5365

5370

5375

5380

5385

5390

5395

5400

5405

5410

5415

5420

5425

5430

5435

5440

5445

5450

5455

5460

5465

5470

5475

5480

5485

5490

5495

5500

5505

5510

5515

5520

5525

5530

5535

5540

5545

5550

5555

5560

5565

5570

5575

5580

5585

5590

5595

5600

5605

5610

5615

5620

5625

5630

5635

5640

5645

5650

5655

5660

5665

5670

5675

5680

5685

5690

5695

5700

5705

5710

5715

5720

5725

5730

5735

5740

5745

5750

5755

5760

5765

5770

5775

5780

5785

5790

5795

5800

5805

5810

5815

5820

5825

5830

5835

5840

5845

5850

5855

5860

5865

5870

5875

5880

5885

5890

5895

5900

5905

5910

5915

5920

5925

5930

5935

5940

5945

5950

5955

5960

5965

5970

5975

5980

5985

5990

5995

6000

6005

6010

6015

6020

6025

6030

6035

6040

6045

6050

6055

6060

6065

6070

6075

6080

6085

6090

6095

6100

6105

6110

6115

6120

6125

6130

6135

6140

6145

6150

6155

6160

6165

6170

6175

6180

6185

6190

6195

6200

6205

6210

6215

6220

6225

6230

6235

6240

6245

6250

6255

6260

6265

6270

6275

6280

6285

6290

6295

6300

6305

6310

6315

6320

6325

6330

6335

6340

6345

6350

6355

6360

6365

6370

6375

6380

6385

6390

6395</p

TABLE 1 (continued)

5

10

15

20

25

30

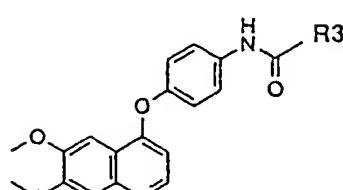
35

40

45

50

55



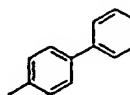
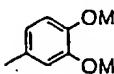
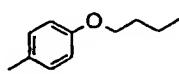
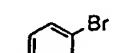
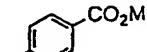
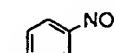
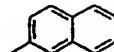
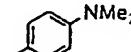
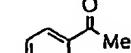
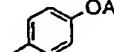
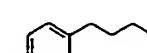
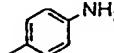
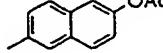
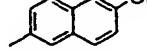
	Compound No.	R3	Compound No.	R3
61		73		
62		74		
63		75		
64		76		
65		77		
66		78		
67		79		
68		80		
69		81		
70		82		
71		83		
72		84		

TABLE 1 (continued)

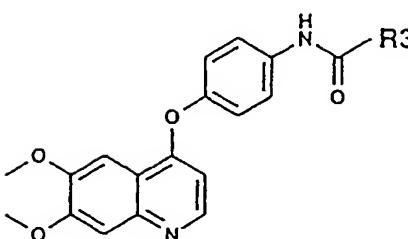
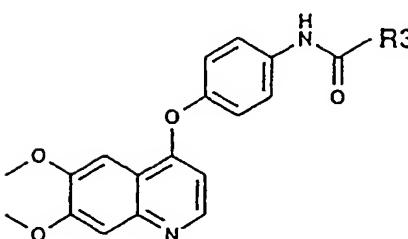
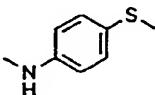
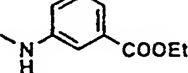
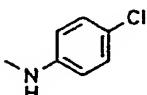
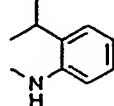
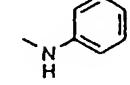
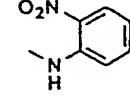
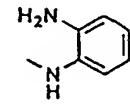
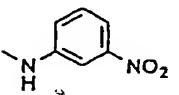
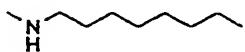
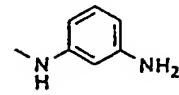
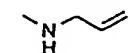
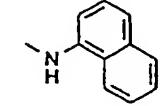
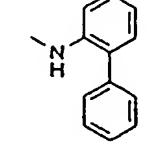
5		
10		
15	Compound No.	R3
20	163	
25	164	
30	165	
35	166	
40	167	
45	168	
50	169	
55	170	
	171	
	172	
	173	
	174	
	175	

TABLE 1 (continued)

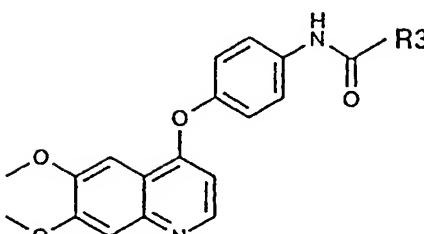
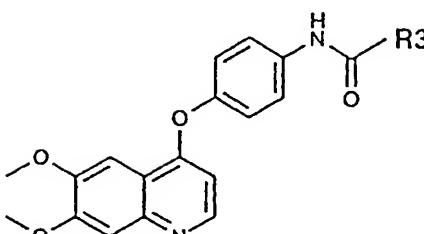
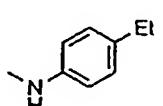
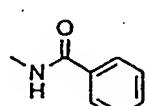
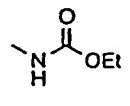
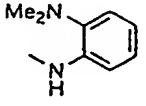
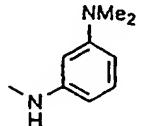
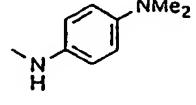
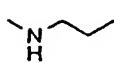
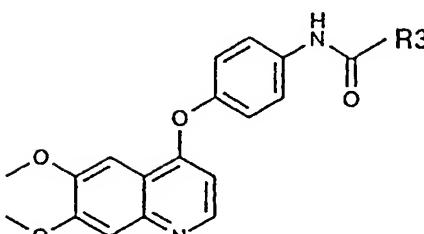
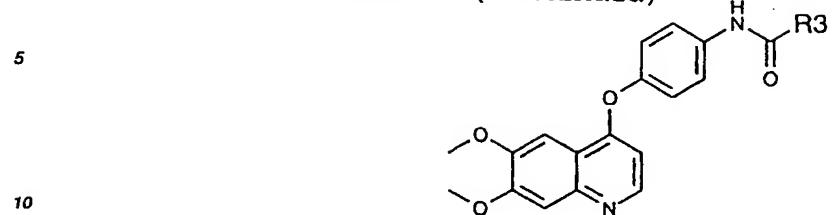
5		
10		
15	Compound No.	R3
20	188	
25	189	
30	190	
35	191	
40	192	
45	193	
50	194	
55		

TABLE 1 (continued)

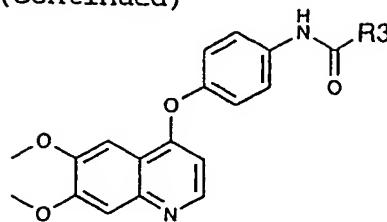


	Compound No.	R3	Compound No.	R3
15	222		229	
20	223		230	
25	224		231	
30	225		232	
35	226		233	
40	227		234	
45	228		235	

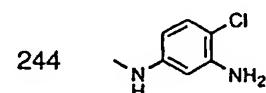
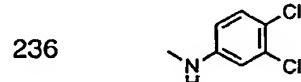
TABLE 1 (continued)

5

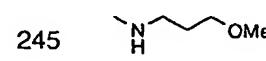
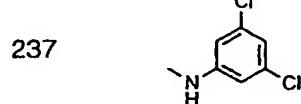
10



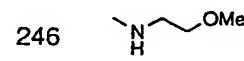
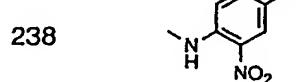
15



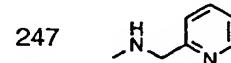
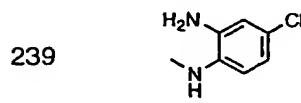
20



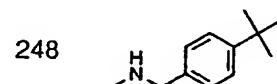
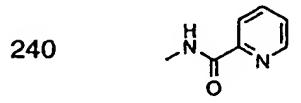
25



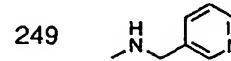
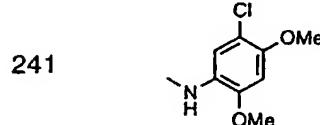
30



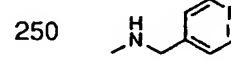
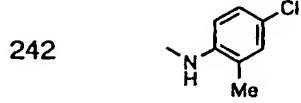
35



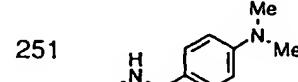
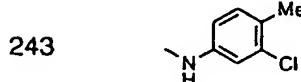
40



45



50

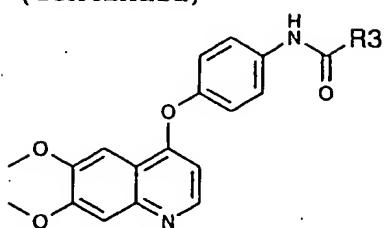


55

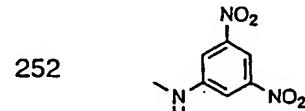
TABLE 1 (continued)

5

10



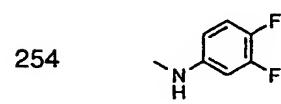
15



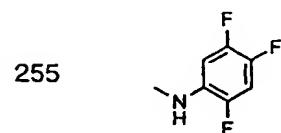
20



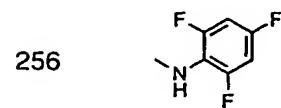
25



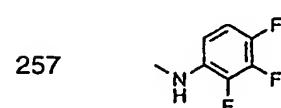
30



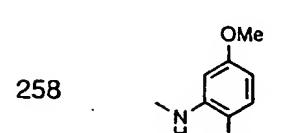
35



40



45



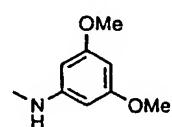
50

55

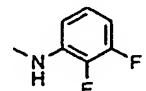
R3

Compound No. R3

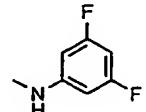
259



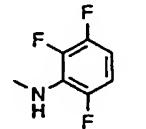
260



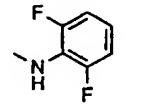
261



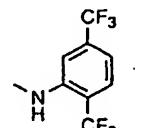
262



263



264



265

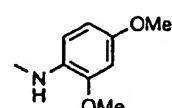
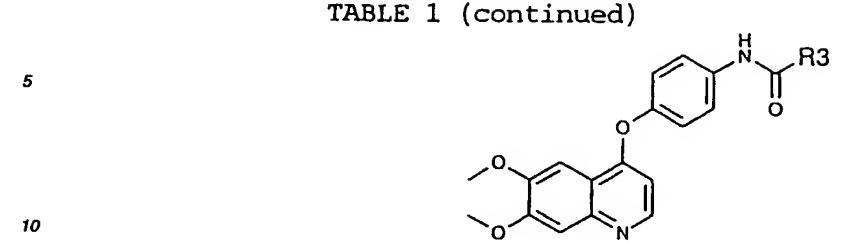
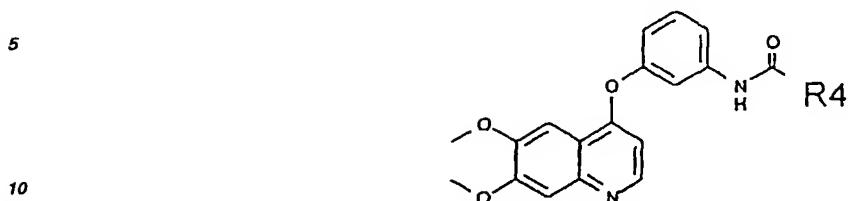


TABLE 1 (continued)



	Compound No.	R3	Compound No.	R3
15	266		275	
20	267		276	
25	268		277	
30	269		278	
35	270		279	
40	271		280	
45	272		281	
50	273		282	
55	274		283	

TABLE 1 (continued)



	Compound No.	R4	Compound No.	R4
15	85		92	
20	86		93	
25	87		94	
30	88		95	
	89		96	
35	90		97	
40	91		98	
45				

50

55

TABLE 1 (continued)

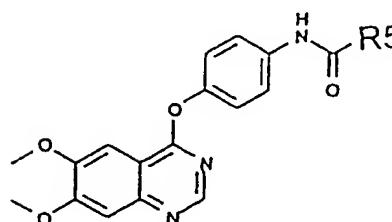
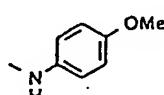
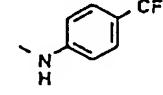
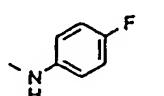
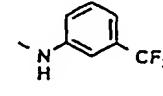
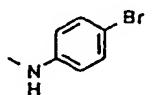
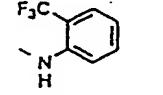
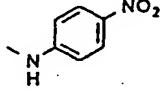
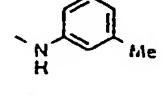
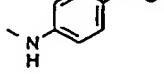
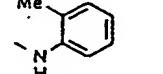
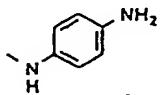
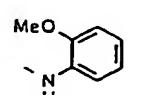
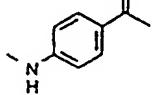
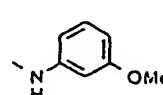
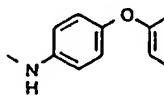
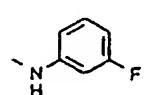
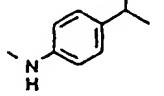
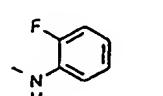
5				
10	Compound No.	R5	Compound No.	R5
15	99		108	
20	100		109	
25	101		110	
30	102		111	
35	103		112	
40	104		113	
45	105		114	
50	106		115	
	107		116	

TABLE 1 (continued)

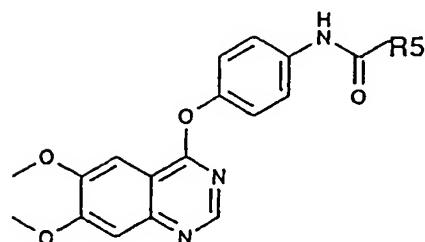
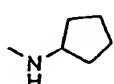
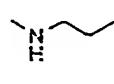
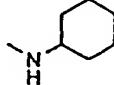
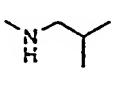
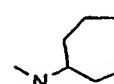
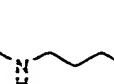
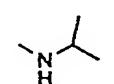
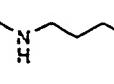
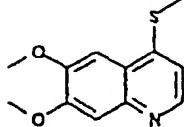
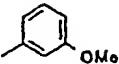
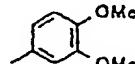
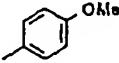
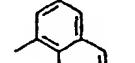
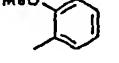
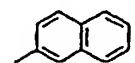
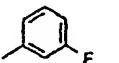
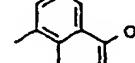
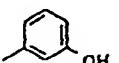
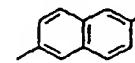
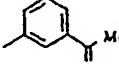
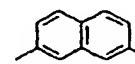
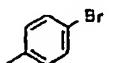
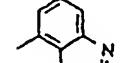
5				
10	Compound No.	R5	Compound No.	R5
15				
20	214		218	
25	215		219	
30	216		220	
35	217		221	
40				
45				
50				
55				

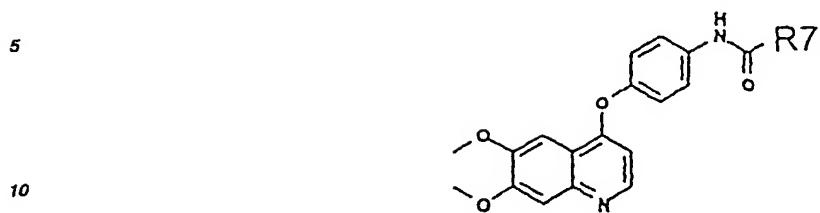
TABLE 1 (continued)

		R6		R6
5				
10				
	Compound No.	R6	Compound No.	R6
15	117		124	
20	118		125	
25	119		126	
30	120		127	
35	121		128	
40	122		129	
45	123		130	

50

55

TABLE 1 (continued)

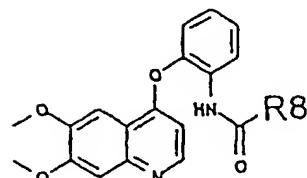


	Compound No.	R7	Compound No.	R7
15	131		136	
20	132		137	
25	133		138	
	134		139	
30	135		140	
35				
40				
45				
50				
55				

TABLE 1 (continued)

5

10



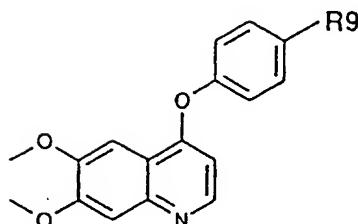
	Compound No.	R8		Compound No.	R8
15	141			148	
20	142			149	
25	143			150	
30	144			151	
35	145			152	
40	146			153	
45	147			154	

50

55

TABLE 1 (continued)

5



10

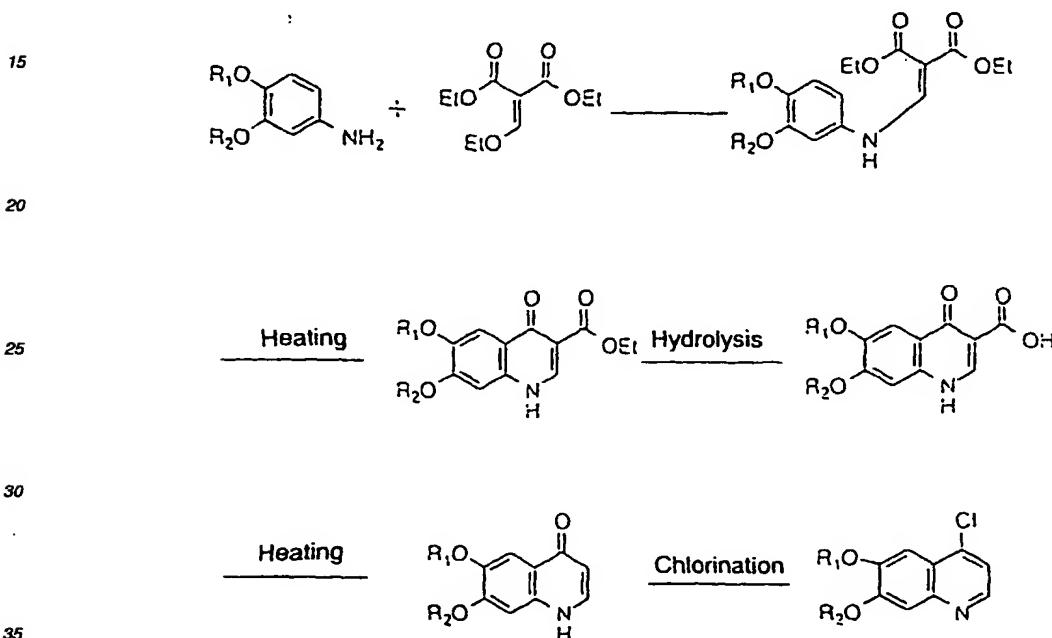
Compound No.	R9	Compound No.	R9
200		207	
201		208	
202		209	
203		210	
204		211	
205		212	
206		213	

55

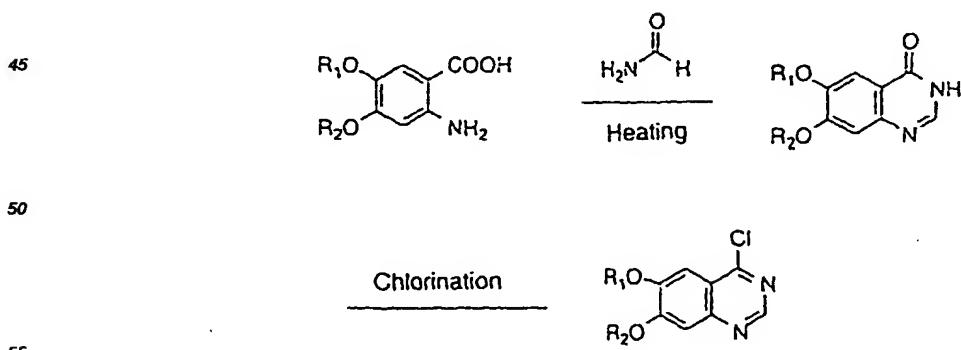
II. Methods of producing compounds of the present invention

Compounds of the present invention can be synthesized, for example, according to the methods described below. However, it should be understood that methods of producing compounds of the present invention are not limited to these methods.

Although all of the compounds of the present invention are novel compounds which are not described in the literature, they can be produced using known chemical techniques. Further, the raw materials used for the production may be commercially available or synthesized by customary methods, if necessary. For example, 4-chloroquinoline derivatives can be synthesized by various known methods. For example, the method described in Org. Synth. Col. Vol. 3, 272 (1955) and Acta Chim. Hung. 112, 241 (1983) can be used. Many quinoline derivatives used in Examples hereinafter can be produced according to the following reaction scheme:



4-Chloroquinazoline derivatives can also be synthesized by various known methods. For example, the methods described in Dai Yuki Kagaku (Comprehensive Organic Chemistry), Vol. 17, 150, edited by Kotake, Asakura Shoten (1967) can be used. Many quinazoline material compounds used in Examples hereinafter can be produced according to the following reaction scheme:



General methods of producing compounds of the present invention will be explained as follows:

1. Compounds of formula (I) wherein Q is represented by formula (II), formula (III) or formula (IV)

a. Synthesis of a compound wherein X is O:

5 A compound of formula (I) wherein X is O is produced by condensation of an aryl compound or heteroaryl compound having a hydroxyl group with a 4-chloroquinoline derivative.

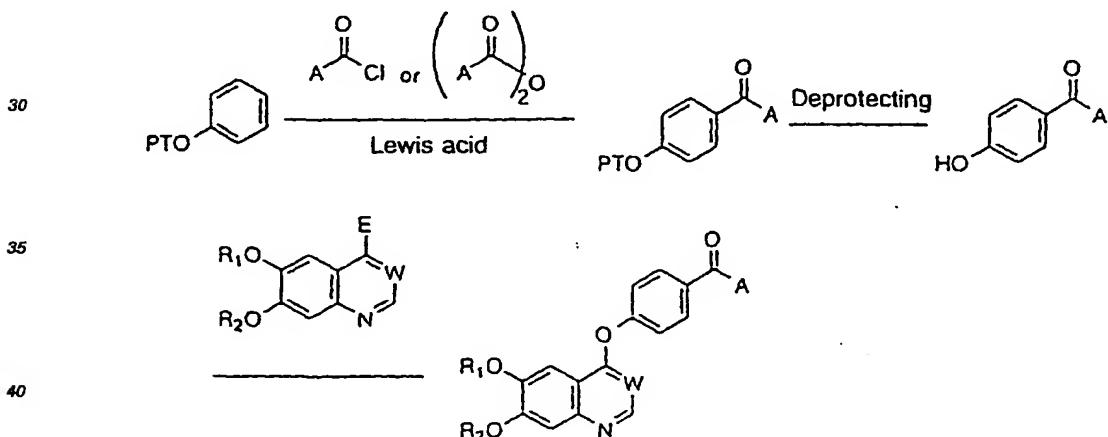
b. Synthesis of compounds wherein X is S:

10 A compound of formula (I) wherein X is S is produced in the same manner as described for a compound wherein X is O, by condensation of an aryl compound or heteroaryl compound having a thiol group with a 4-chloroquinoline derivative.

2. Compounds of formula (I) wherein Q is represented by formula (V) wherein both j and k are 0

15 a. Synthesis of a compound wherein X is O:

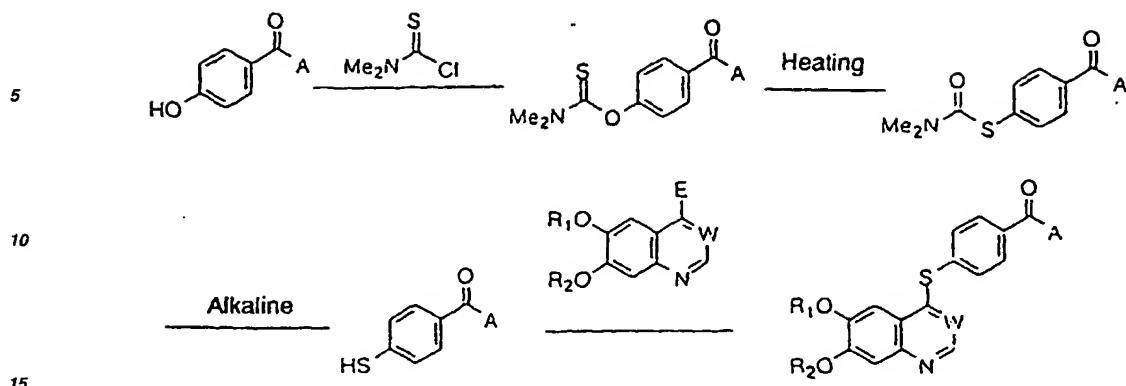
20 A Friedel-Crafts acylation reaction is carried out with phenol with a protected hydroxyl group by an appropriate protecting group in the presence of a Lewis acid (e.g., rare earth trifluoromethanesulfonate, in particular, scandium (III) trifluoromethanesulfonate or ytterbium (III) trifluoromethanesulfonate) described in literatures (e.g., J. Chem. Soc., Chem. Commun., 1157 (1993); Synlett, 1157 (1994)) to obtain an acylated compound. Next, the protecting group of the hydroxyl group of the acylated compound is removed, and the resultant compound is reacted with a 4-chloroquinoline derivative or 4-chloroquinazoline derivative at a temperature between 80 and 200 °C, preferably between 130 and 180 °C in no solvent or in the presence of an appropriate polar solvent for 1 minute to 5 hours, preferably for 10 minutes to 25 1 hour to obtain the target compound.



45 [In the formulas, A, R₁, R₂ and W are defined as described above, E is a leaving group (e.g., halogen, methanesulfonate, p-toluenesulfonate or trifluoromethanesulfonate, preferably chlorine), and PT is a protecting group (e.g., methyl or methoxymethyl)].

b. Synthesis of a compound wherein X is S:

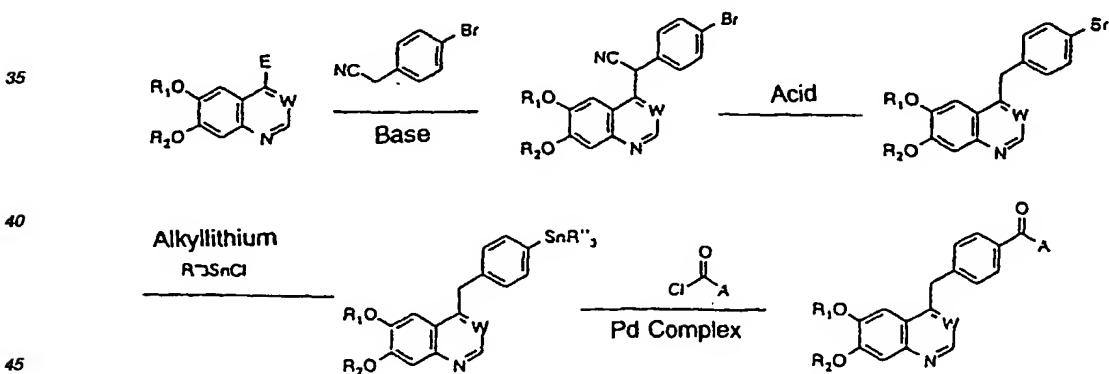
50 For example, an acylthiophenol derivative can be synthesized by the following method described in the literature (Org. Syn. 51, 139 (1971)). Namely, an acyphenol derivative which can be synthesized as described in a. above is reacted with N,N-dimethylthiocarbamoylchloride to synthesize an O-aryl-N,N-dimethylthiocarbamate derivative. This derivative is heated (for example, at 200-300 °C) so that an S-aryl-N,N-dimethylthiocarbamate derivative with rearranged oxygen and sulfur is formed in situ, which is then treated under alkaline conditions to yield the corresponding acylthiophenol derivative. Next, in the same manner as described for producing a compound wherein X is O, or in a polar solvent (e.g., N,N-dimethylformamide), the acylthiophenol derivative is reacted with a 4-chloroquinoline derivative or 4-chloroquinazoline derivative with sodium hydroxide at a temperature between 80 and 150 °C to obtain the target compound.



[In the formulas, A, R₁, R₂, W and E are defined as described above].

c. Synthesis of a compound wherein X is CH₂:

20 A compound represented by formula (I) wherein X is CH₂ can be synthesized using the method described by R. Cutler et al. (J. Am. Chem. Soc. **71**, 3375 (1949)). In the present method, a 4-chloroquinoline derivative or 4-chloroquinazoline derivative is added to 4-bromophenylacetonitrile sodium salt in an appropriate organic solvent (e.g., toluene), then refluxed, and the diaryl-substituted acetonitrile so obtained is isolated and purified. The purified product is dissolved in an acidic solvent (e.g., aqueous sulfuric acid) and refluxed for 1-20 hours to obtain a 4-(4-bromobenzyl)quinoline derivative or said quinazoline derivative. Next, using the method of J. K. Stille et al. (J. Org. Chem. **48**, 4634 (1983)), the 4-(4-bromobenzyl)quinoline derivative or said quinazoline derivative is reacted with alkylolithium in an appropriate solvent (e.g., tetrahydrofuran) to form an organic lithium compound in situ. Trialkyltin chloride is then added to yield an organic tin compound, and the resulting compound and an acid chloride are refluxed with heat in an appropriate organic solvent (e.g., chloroform) in the presence of a catalytic amount of a palladium complex (e.g., bis(triphenylphosphine)palladium(II) chloride) to produce the target compound.



[In the formulas, A, R₁, R₂, W and E are defined as described above, and R^a is methyl or butyl].

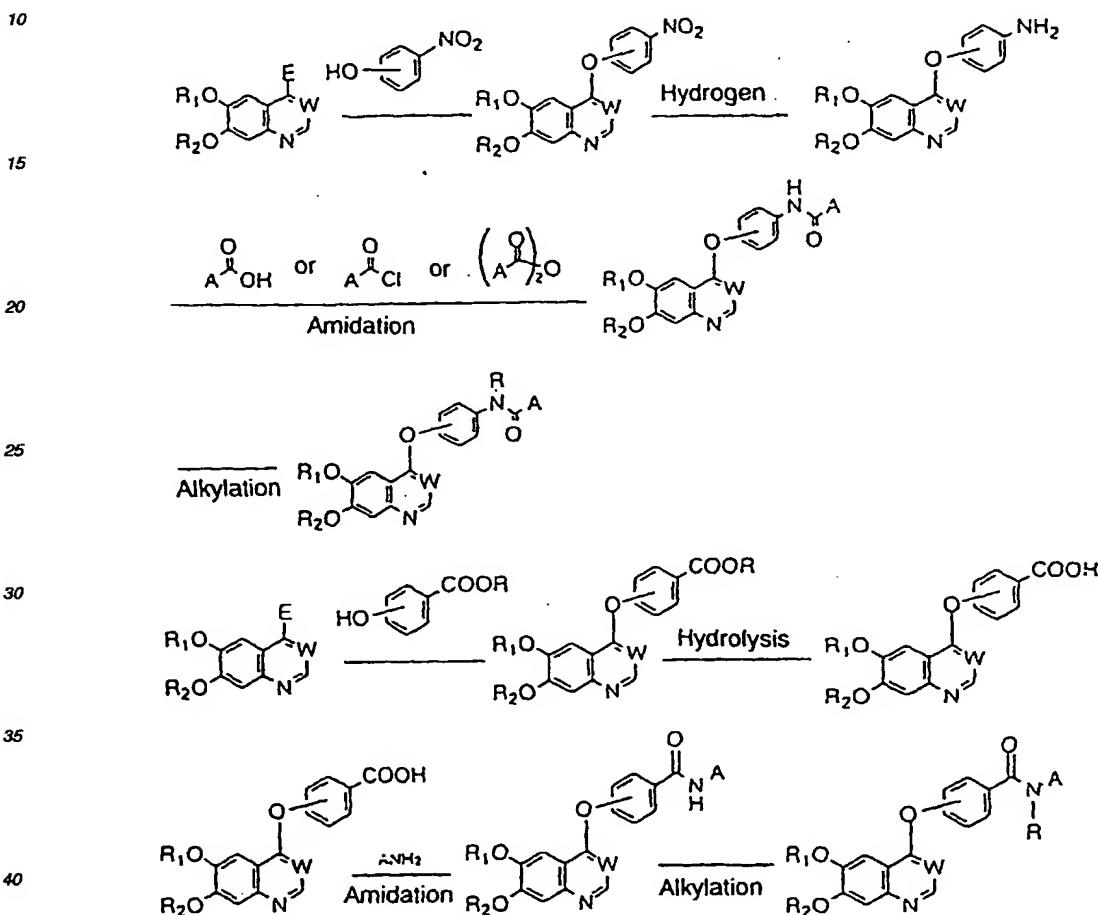
50 3. Compounds of formula (I) wherein Q is represented by formula (V) wherein B is O, and j is 1 and k is 0, or j is 0 and k is 1

a. Synthesis of a compound wherein X is O:

55 A 4-chloroquinoline derivative or 4-chloroquinazoline derivative is reacted with nitrophenol in an appropriate solvent or no solvent to synthesize a 4-(nitrophenoxy)quinoline derivative or said quinazoline derivative. The resulting derivative is then stirred in an appropriate solvent (e.g., N,N-dimethylformamide) in the presence of a catalyst (e.g., palladium hydroxide/carbon) under a hydrogen atmosphere to obtain the 4-(aminophenoxy)quinoline derivative or said

quinazoline derivative. The resulting derivative can be amidated using carboxylic acids or their derivatives to produce the target compound according to known methods. Further, its N-alkylamides can be produced by reaction with an alkyl halide in an appropriate solvent (e.g., N,N-dimethylformamide) in the presence of a base (e.g., sodium hydride).

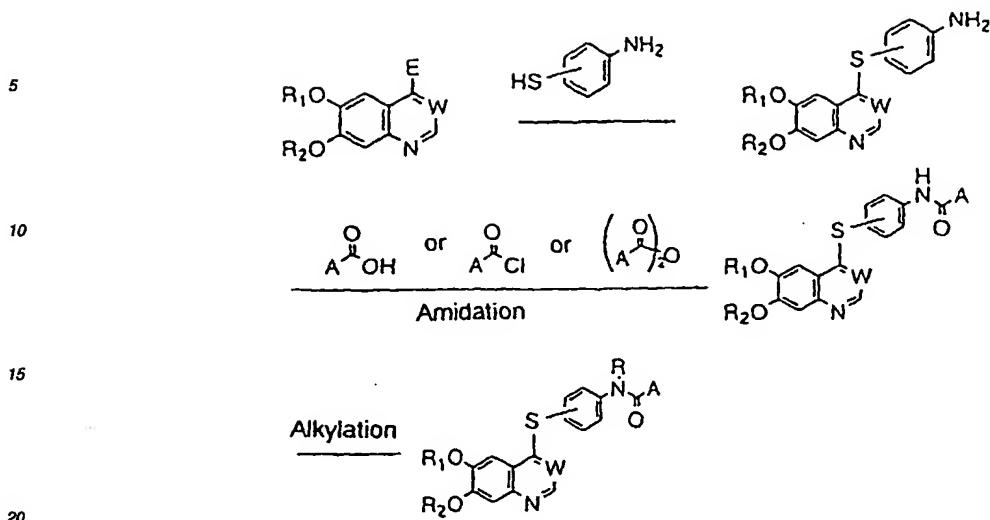
Further, analogously, a 4-(carboxyphenoxy)quinoline derivative or said quinazoline derivative can be obtained by reacting a hydroxybenzoic acid ester with a 4-chloroquinoline derivative or 4-chloroquinazoline derivative, followed by acid or base hydrolysis. The resultant derivative can be amidated using an alkylamine or arylamine to produce the target compound according to known methods. Further, its N-alkylamides can be produced by the abovementioned method.



45 [In the formulas, A, R₁, R₂, W and E are defined as described above, and R is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl or t-butyl.]

b. Synthesis of a compound wherein X is S:

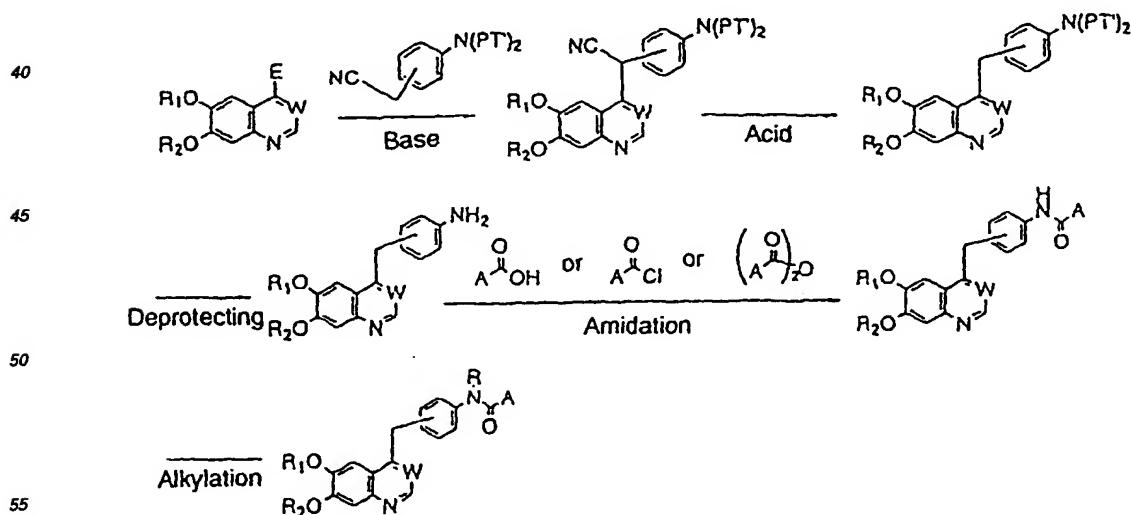
50 A 4-(aminophenylthio)quinoline derivative or said quinazoline derivative is obtained by reacting a 4-chloroquinoline derivative or 4-chloroquinazoline derivative with aminothiophenol in an appropriate solvent or no solvent. The resulting derivative can be amidated using carboxylic acids or their derivatives to produce the target compound according to known methods. Further, its N-alkylamides can be produced by reaction with an alkyl halide in an appropriate solvent (e.g., N,N-dimethylformamide) in the presence of a base (e.g., sodium hydride).



[In the formulas, A, R_1 , R_2 , W, E and R are defined as described above.]

25 c. Synthesis of a compound wherein X is CH_2 :

A compound represented by formula (I) wherein X is CH_2 can be synthesized by the method described by R. Cutler et al. (J. Am. Chem. Soc. 71, 3375 (1949)). In this method, a base (e.g., sodium hydride) is added to aminophenylacetonitrile with a protected amino group (e.g., by a benzyl group) in an appropriate organic solvent (e.g., toluene), a 4-chloroquinoline derivative or 4-chloroquinazoline derivative is added, and the mixture is refluxed. The diaryl-substituted acetonitrile so obtained is isolated and purified, then dissolved in an acidic solvent (e.g., aqueous sulfuric acid) and refluxed for 1-20 hours, and then the protecting group is removed to obtain a 4-(aminobenzyl)quinoline derivative or 4-(aminobenzyl)quinazoline derivative. The resulting derivative can be amidated using carboxylic acids or their derivative to produce the target compound according to known methods. Further, its N-alkylamides can be produced by reaction with an alkyl halide in an appropriate solvent (e.g., N,N-dimethylformamide) in the presence of a base (e.g., sodium hydride).



[In the formulas, A, R₁, R₂, W, E and R are defined as described above, and PT' is a protecting group (e.g., benzyl)]

group.]

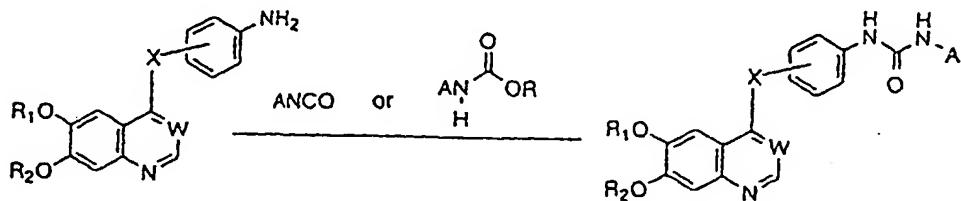
4. Compounds of formula (I) in which Q is represented by formula (V) wherein both j and k are 1

5 a. Synthesis of a compound wherein B is O:

A compound wherein B is O can be produced by reacting one of the abovementioned intermediates with an isocyanate derivative or carbamate derivative according to known methods.

10

15



20

b. Synthesis of a compound wherein B is S:

A compound wherein B is S can be produced by reacting one of the abovementioned intermediates with an isocyanate derivative or thiocarbamate derivative according to known methods.

25

30

35

[In the formulas, A, R₁, R₂, W and R are defined as described above, and X is O, S or CH₂.]

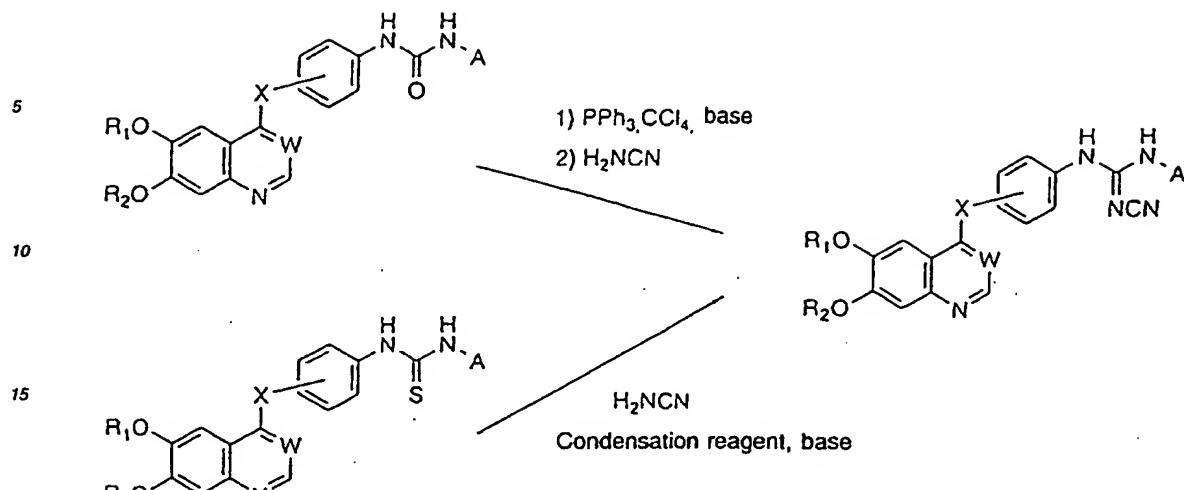
c. Synthesis of a compound wherein B is NCN:

40 A compound wherein B is NCN can be produced according to the method described by H. J. Petersen et al. (J. Med. Chem. 21, 773 (1978)).

In this method, the compound obtained in the abovementioned a. is refluxed in the presence of a triphosphorus compound (e.g., triphenylphosphine), a base (e.g., triethylamine) and carbon tetrachloride in an appropriate organic solvent (e.g., methylene chloride) to produce the corresponding carbodiimide, and then the carbodiimide is reacted with cyanamide to obtain the target compound. Alternatively, the target compound can be produced by reacting the compound obtained in the abovementioned b. with cyanamide in the presence of a condensation reagent (e.g., dicyclohexylcarbodiimide) and a base (e.g., ethyldiisopropylamine) in an appropriate organic solvent (e.g., ether).

50

55



[In the formulas, A, R₁, R₂ and W are defined as described above, and X is O, S or CH₂.]

Salts of the quinoline derivatives or quinazoline derivatives obtained by the methods of the abovementioned 1-4 can be produced by general methods which are conventionally used to produce salts.

III. Use of compounds of the present invention

Intracellular signal transduction mediated by growth factor receptor autophosphorylation is involved in various pathophysiological situations including neoplastic or other abnormal cell growth. Since quinoline derivatives and quinazoline derivatives of the present invention and their pharmaceutically acceptable salts have an inhibitory activity on platelet-derived growth factor (PDGF) receptor autophosphorylation, they are expected to be useful as a therapeutic agent to treat various diseases which are caused by abnormal cell growth generated by PDGF receptor autophosphorylation due to an excessive amount of PDGF (e.g., leukemia, cancers, psoriasis, glomerular nephritis, organofibrosis, atherosclerosis, restenosis after percutaneous coronary angioplasty or bypass surgery and rheumatoid arthritis).

Pharmaceutical compositions which contain compounds of the present invention as an effective component, namely medicinal compositions, can be administered to human and other animals either orally or non-orally (e.g., intravenous, intramuscular, subcutaneous, rectal or endermic administration). Accordingly, medicinal compositions which contain compounds of the present invention as an effective component are prepared into a suitable dosage form depending on the method of administration.

Examples of oral preparations include tablets, capsules, powders, granules and syrups, and examples of non-oral preparations include injections, rectal agents, oily suppositories and aqueous suppositories.

These various pharmaceutical preparations can be produced using ordinarily excipients, disintegrating agents, binding agents, lubricating agents, coloring agents, diluents or release controlling agents.

Examples of excipients are lactose, glucose, corn starch, sorbitol, and crystalline cellulose; examples of disintegrating agents are starch, sodium alginate, gelatine powder, calcium carbonate, calcium citrate and dextrose; examples of bonding agents are dimethylcellulose, polyvinyl alcohol, polyvinyl ether, methycellulose, ethylcellulose, gum arabic, gelatine, hydroxypropylcellulose and polyvinylpyrrolidone; examples of lubricating agents are talc, magnesium stearate, polyethylene glycol and hydrogenated vegetable oils.

Further, the abovementioned injectable agents can be produced by adding buffering agents, pH controlling agents, stabilizing agents or the like, if necessary.

Contents of the compounds of the present invention in the medicinal formulations vary depending on their dosage form, but they are generally between about 0.5 and 50% by weight, preferably between about 1 and 20% by weight of the total.

The particular dose for each individual patient is determined as a function of age, body weight and sex of the patient, type or severity of the disease to be treated. For example, a daily dose of between 1 and 100 mg/kg of body weight, preferably between 1 and 50 mg/kg of body weight, is administered one or more times.

Examples

The present invention is illustrated in greater detail by the following Examples and Test Examples. The numbers in parentheses at the end of title compound in the Examples correspond to the compound numbers given in Table 1.

5

Example 1 (Reference Example)

6-Methoxy-2-naphthol

10 Potassium carbonate (1.244 g) was added to a solution of commercially available 2,6-dihydroxynaphthalene (961 mg) in N,N-dimethylformamide (100 ml), and the admixture was stirred at room temperature for 30 minutes. Dimethyl sulfate (1.14 ml) was slowly added dropwise to the mixture and the resulting mixture was further stirred at room temperature overnight. The reaction mixture thus prepared was neutralized with a 2N HCl solution and then partitioned between water and ethyl acetate, and the ethyl acetate layer was dried with anhydrous magnesium sulfate. After removing the solvent by distillation under reduced pressure, the resulting residue was purified by column chromatography on silica gel (eluting with chloroform/ethyl acetate) to obtain 307 mg of the title compound (yield: 29%).

15 ¹H-NMR (CDCl₃, 90MHz) : δ 3.89 (s, 3H), 7.00~7.18 (m, 4H), 7.53~7.70 (m, 2H) Mass spectrometry data (FD-MS, m/z) : 174 (M⁺)

20

Example 2

6,7-Dimethoxy-4-(6-methoxy-2-naphthyl)quinoline [12]

25 4-Chloro-6,7-dimethoxyquinoline (75 mg) and 6-methoxy-2-naphthol (174 mg) obtained in Example 1 were mixed and stirred at 180 °C for 30 minutes, and the reaction mixture was then purified by thin layer chromatography on silica gel (eluting with hexane/acetone (2/1)) to obtain 71 mg of the title compound (yield: 59%).

30 ¹H-NMR (CDCl₃, 90MHz) : δ 3.96 (s, 3H), 4.07 (s, 3H), 4.08 (s, 3H), 6.53 (d, J=5.71Hz, 1H), 7.18~7.36 (m, 3H), 7.56~7.91 (m, 5H), 8.50 (br, 1H)
Mass spectrometry data (FD-MS, m/z) : 361 (M⁺)

Example 3

6,7-Dimethoxy-4-(2-naphthyl)quinoline [10]

35 4-Chloro-6,7-dimethoxyquinoline (45 mg) and commercially available β-naphthol (144 mg) were mixed and stirred at 180 °C for 2 hours, and the reaction mixture was then purified in the same manner as described in Example 2 to obtain 45 mg of the title compound (yield: 68%).

40

¹H-NMR (CDCl₃, 90MHz) : δ 4.05 (s, 3H), 4.06 (s, 3H), 6.52 (d, J=5.28Hz, 1H), 7.27~7.61 (m, 6H), 7.75~8.00 (m, 3H), 8.50 (br, 1H)
Mass spectrometry data (FD-MS, m/z) : 331 (M⁺)

45 Example 4

6,7-Dimethoxy-4-(7-methoxy-2-naphthyl)quinoline [13]

50 4-Chloro-6,7-dimethoxyquinoline (89 mg) and commercially available 7-methoxy-2-naphthol (209 mg) were mixed and stirred at 180 °C for 30 minutes, and the reaction mixture was then purified in the same manner as described in Example 2 to obtain 59 mg of the title compound (yield: 41%).

55 ¹H-NMR (CDCl₃, 90MHz) : δ 3.92 (s, 3H), 4.05 (s, 3H), 4.07 (s, 3H), 6.54 (d, J=5.49Hz, 1H), 7.10~7.24 (m, 3H), 7.49~7.91 (m, 5H), 8.49 (d, J=5.49, 1H)
Mass spectrometry data (FD-MS, m/z) : 361 (M⁺)

Example 5 (Reference Example)

5-Methoxy-1-naphthol

5 Using commercially available 1,5-dihydroxynaphthalene, the synthesis and purification were carried out in the same manner as described in Example 1 to obtain the title compound (yield: 28%).

¹H-NMR (CDCl₃, 90MHz) : δ 4.00 (s, 3H), 6.79~6.89 (m, 2H), 7.30~7.48 (m, 2H), 7.69~7.90 (m, 2H)
 Mass spectrometry data (FD-MS, m/z) : 174 (M⁺)

10

Example 6

6,7-Dimethoxy-4-(5-methoxy-1-naphthoxy)quinoline [11]

15 4-Chloro-6,7-dimethoxyquinoline (85 mg) and 5-methoxy-1-naphthol (67 mg) obtained in Example 5 were mixed and stirred at 180 °C for 20 minutes, and the reaction mixture was then purified in the same manner as described in Example 2 to obtain 19 mg of the title compound (yield: 14%).

¹H-NMR (CDCl₃, 90MHz) : δ 4.04 (s, 3H), 4.08 (s, 6H), 6.31 (d, J=5.27Hz, 1H), 6.83~6.92 (m, 1H), 7.34~7.61 (m, 4H), 7.75 (s, 1H), 8.20~8.29 (s, 1H), 8.43 (brs, 1H)
 Mass spectrometry data (FD-MS, m/z) : 361 (M⁺)

Example 7

6,7-Dimethoxy-4-(4-indolyloxy)quinoline [17]

40 4-Chloro-6,7-dimethoxyquinoline (112 mg) and commercially available 4-hydroxyindole (200 mg) were mixed and stirred at 180 °C for 30 minutes. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and chloroform, and the chloroform layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (3/1) to obtain 51 mg of the title compound (yield: 32%).

¹H-NMR (CDCl₃, 90MHz) : δ 3.95 (s, 3H), 3.96 (s, 3H), 6.08~6.13 (m, 1H), 6.35 (d, J=5.28Hz, 1H), 6.83~6.93 (m, 1H), 7.29~7.45 (m, 5H), 7.62 (s, 1H), 8.40 (d, J=5.05Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 320 (M⁺)

Example 8

6,7-Dimethoxy-4-(3,4-dimethoxyphenoxy)quinoline [8]

45 4-Chloro-6,7-dimethoxyquinoline (90 mg) and commercially available 3,4-dimethoxyphenol (187 mg) were mixed and stirred at 180 °C for 30 minutes, and the mixture was then purified by column chromatography on silica gel eluting with hexane/acetone to obtain 26 mg of the title compound (yield: 19%).

50

¹H-NMR (CDCl₃, 500MHz) : δ 3.87 (s, 3H), 3.93 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.45 (d, J=4.9Hz, 1H), 6.75 (dd, J=2.4Hz, 9.2Hz, 1H), 6.75 (d, J=2.4Hz, 1H), 6.93 (d, J=9.2Hz, 1H), 7.42 (s, 1H), 7.57 (s, 1H), 8.48 (d, J=4.9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 341 (M⁺)

Example 9

6,7-Dimethoxy-4-(6-quinolyloxy)quinoline [15]

55 Using 4-chloro-6,7-dimethoxyquinoline (90 mg) and commercially available 6-hydroxyquinoline (176 mg), reaction and purification were carried out in the same manner as described in Example 8 to obtain 62 mg of the title compound (yield: 46%).

¹H-NMR (CDCl₃, 500MHz) : δ 4.05 (s, 3H), 4.06 (s, 3H), 6.56 (d, J=5.5Hz, 1H), 7.44~7.62 (m, 5H), 8.13 (d, J=8.5Hz, 1H), 8.22 (d, J=9.2Hz, 1H), 8.53 (d, J=4.9Hz, 1H), 8.94 (d, J=4.3Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 332 (M⁺)

5 Example 10

6,7-Dimethoxy-4-(3-fluorophenoxy)quinoline [4]

10 4-Chloro-6,7-dimethoxyquinoline (100 mg) and commercially available 3-fluorophenol (0.20 ml) were mixed and stirred at 180 °C for 30 minutes. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate and then with chloroform to obtain 125 mg of the title compound (yield: 94%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 4.04 (s, 3H), 4.06 (s, 3H), 6.56 (d, J=4.9Hz, 1H), 6.93 (d, J=9.2Hz, 1H), 6.95~7.05 (m, 2H), 7.39~7.45 (m, 1H), 7.47 (s, 1H), 7.50 (s, 1H), 8.53 (d, J=4.3Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 299 (M⁺)

20 Example 11

6,7-Dimethoxy-4-(3-hydroxyphenoxy)quinoline [5]

25 4-Chloro-6,7-dimethoxyquinoline (300 mg) and commercially available resorcinol monoacetate (0.835 ml) were mixed and stirred at 180 °C for 30 minutes. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was crystallized with chloroform to obtain 37 mg of the title compound (yield: 9%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 4.01 (s, 3H), 4.02 (s, 3H), 6.48 (t, J=2.4Hz, 1H), 6.59 (d, J=5.5Hz, 1H), 6.77 (dd, J=2.4Hz, 7.3Hz, 1H), 6.82 (dd, J=2.4Hz, 8.6Hz, 1H), 7.33 (t, J=7.9Hz, 1H), 7.39 (s, 1H), 7.47 (s, 1H), 8.40 (d, J=5.5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 297 (M⁺)

35 Example 12

6,7-Dimethoxy-4-(4-bromophenoxy)quinoline [7]

40 4-Chloro-6,7-dimethoxyquinoline (1.00 g) and commercially available 4-bromophenol (115 mg) were mixed and stirred at 180 °C for 40 minutes. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and chloroform, and the chloroform layer was washed with brine and dried with sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel, eluting in sequence with hexane/acetone, chloroform and chloroform/methanol, to obtain 1.20 g of the title compound (yield: 76%).

45 ¹H-NMR (CDCl₃, 500MHz) : δ 4.04 (s, 3H), 4.05 (s, 3H), 6.48 (d, J=4.9Hz, 1H), 7.08 (d, J=8.5Hz, 2H), 7.43 (s, 1H), 7.51 (s, 1H), 7.58 (d, J=8.5Hz, 2H), 8.51 (d, J=4.9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 359 (M⁺), 361 (M⁺+2)

50 Example 13

6,7-Dimethoxy-4-(2-methoxyphenoxy)quinoline [1]

4-Chloro-6,7-dimethoxyquinoline (102 mg) and commercially available 2-methoxyphenol (0.5 ml) were mixed and stirred at 150 °C for 8 hours. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting first with hexane/ethyl acetate and then with chloroform/methanol to obtain

76 mg of the title compound (yield: 54%).

¹H-NMR (CDCl₃, 90MHz) : δ 3. 78 (s, 3H), 4. 05 (s, 3H), 4. 05 (s, 3H), 6. 31 (d, J=5. 3Hz, 1H), 6. 9~7. 4 (m, 4H), 7. 42 (s, 1H), 7. 63 (s, 1H), 8. 45 (d, J=5. 3Hz, 1H)

5 Mass spectrometry data (FAB-MS, m/z) : 312 (M⁺+1)

Example 14

6,7-Dimethoxy-4-(3-methoxyphenoxy)quinoline [2]

10 4-Chloro-6,7-dimethoxyquinoline (103 mg) and commercially available 3-methoxyphenol (158 mg) were mixed and stirred at 160 °C for 9 hours. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate to obtain 29 mg of the title compound (yield: 52%).

15 ¹H-NMR (CDCl₃, 90MHz) : δ 3. 82 (s, 3H), 4. 04 (s, 3H), 4. 05 (s, 3H), 6. 53 (d, J=5. 3Hz, 1H), 6. 7~6. 9 (m, 3H), 7. 35 (t, J=7. 0Hz, 1H), 7. 43 (s, 1H), 7. 54 (s, 1H), 8. 50 (d, J=5. 3Hz, 1H)

16 Mass spectrometry data (FD-MS, m/z) : 311 (M⁺)

20 Example 15

6,7-Dimethoxy-4-(4-methoxyphenoxy)quinoline [3]

25 4-Chloro-6,7-dimethoxyquinoline (103 mg) and commercially available 4-methoxyphenol (286 mg) were mixed and stirred at 150 °C for 6 hours. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and dried with anhydrous sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting first with hexane/ethyl acetate and then with chloroform/ethyl acetate to obtain 2.21 g of the title compound (yield: 88%).

30 ¹H-NMR (CDCl₃, 90MHz) : δ 3. 85 (s, 3H), 4. 05 (s, 3H), 4. 05 (s, 3H), 6. 41 (d, J=5. 3Hz, 1H), 6. 97 (d, J=9. 5Hz, 2H), 7. 14 (d, J=9. 5Hz, 2H), 7. 43 (s, 1H), 7. 58 (s, 1H), 8. 46 (d, J=5. 3Hz, 1H)

35 Mass spectrometry data (FAB-MS, m/z) : 312 (M⁺+1)

Example 16

6,7-Dimethoxy-4-(5-quinolyl)quinoline [14]

40 4-Chloro-6,7-dimethoxyquinoline (50 mg) and commercially available 5-hydroxyquinoline (50 mg) were mixed and stirred at 170 °C for 10 minutes. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by thin layer chromatography on silica gel eluting first with hexane/ethyl acetate (1/1) and then with chloroform/methanol (50/1) to obtain 47 mg of the title compound (yield: 64%).

45 ¹H-NMR (CDCl₃, 90MHz) : δ 4. 06 (s, 3H), 4. 07 (s, 3H), 6. 35 (d, J=5. 3Hz, 1H), 7. 2~7. 5 (m, 3H), 7. 68 (s, 1H), 7. 7~8. 4 (m, 3H), 8. 46 (d, J=5. 3Hz, 1H), 8. 49 (dd, J=1. 76Hz, 4. 17Hz, 1H)

50 Mass spectrometry data (FD-MS, m/z) : 332 (M⁺)

Example 17

6,7-Dimethoxy-4-(1-naphthyl)quinoline [9]

55 4-Chloro-6,7-dimethoxyquinoline (97 mg) and commercially available 1-naphthol (340 mg) were mixed and stirred at 150 °C for 8 hours. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified

by column chromatography on silica gel eluting first with hexane/ethyl acetate (3/1) and then with chloroform/methanol (100/1), and further purified by thin layer chromatography on silica gel eluting with hexane/ethyl acetate (1/1) to obtain 57 mg of the title compound (yield: 40%).

5 ¹H-NMR (CDCl₃, 90MHz) : δ 4. 05 (s, 3H), 4. 05 (s, 3H), 6. 32 (d, J=5. 3Hz, 1H), 7. 2~7. 6 (m, 5H), 7. 74 (s, 1H),
7. 8~8. 0 (m, 3H), 8. 35 (d, J=5. 3Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 331 (M⁺)

Example 18

10 6,7-Dimethoxy-4-(5-indolyloxy)quinoline [16]

15 4-Chloro-6,7-dimethoxyquinoline (1.0 g) and commercially available 5-hydroxyindole (1.19 g) were mixed and stirred at 150 °C for 1.5 hours. The reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and then partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting in sequence with hexane/ethyl acetate, chloroform and chloroform/methanol, to obtain 898 mg of the title compound (yield: 63%).

20 ¹H-NMR (CDCl₃, 90MHz) : δ 4. 05 (s, 3H), 4. 07 (s, 3H), 6. 42 (d, J=5. 3Hz, 1H), 6. 5~6. 7 (m, 1H), 6. 9~7. 6 (m, 5H), 7. 67 (s, 1H), 8. 44 (d, J=5. 3Hz, 1H), 8. 55 (br, 1H)
Mass spectrometry data (FD-MS, m/z) : 320 (M⁺)

Example 19

25 6,7-Dimethoxy-4-(3-methoxyphenylthio)quinoline [117]

30 4-Chloro-6,7-dimethoxyquinoline (50 mg) and commercially available 3-methoxybenzenethiol (77 mg) were mixed and stirred at 180 °C for 30 seconds. Purification was carried out in the same manner as described in Example 18 to obtain 72 mg of the title compound (yield: 100%).

35 ¹H-NMR (CDCl₃, 90MHz) : δ 3. 79 (s, 3H), 4. 01 (s, 3H), 4. 03 (s, 3H), 6. 84 (d, J=4. 8Hz, 1H), 6. 9~7. 5 (m, 6H), 8. 45 (d, J=5. 1Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 327 (M⁺)

Example 20

40 6,7-Dimethoxy-4-(4-methoxyphenylthio)quinoline [118]

45 4-Chloro-6,7-dimethoxyquinoline (50 mg) and commercially available 4-methoxybenzenethiol (63 mg) were mixed and stirred at 150 °C for 5 minutes. Purification was carried out in the same manner as described in Example 18, and further crystallization with chloroform gave 80 mg of the title compound (yield: 100%).

50 ¹H-NMR (CDCl₃, 90MHz) : δ 3. 88 (s, 3H), 4. 03 (s, 3H), 4. 05 (s, 3H), 6. 60 (d, J=4. 8Hz, 1H), 7. 15 (d, J=8. 7Hz, 2H), 7. 38 (s, 1H), 7. 39 (s, 1H), 7. 52 (d, J=8. 8Hz, 2H) 8. 39 (d, J=5. 1Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 327 (M⁺)

Example 21 (Reference Example)

55 4-Bromo-1-methoxymethylphenol

55 Commercially available 4-bromophenol (17.3 g) was dissolved in N,N-dimethylformamide (90 ml), to which sodium hydride (2.64 g) was added while cooled in ice. After stirring at room temperature overnight, chloromethyl methyl ether (8.35 ml) was added, and the admixture was stirred for a further 1 hour. The reaction mixture was partitioned between water and ethyl acetate, and the ethyl acetate layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/acetone to obtain 18.25 g of the title compound (yield: 84%).

¹H-NMR (CDCl₃, 90MHz) : δ 3.46 (s, 3H), 5.13 (s, 2H), 6.91 (d, J=9.2Hz, 2H), 7.38 (d, J=9.2Hz, 2H)
 Mass spectrometry data (FD-MS, m/z) : 216 (M⁺), 218 (M⁺+2)

Example 22 (Reference Example)

5

4-Tri-n-butylin-1-methoxymethylphenol

4-Bromo-1-methoxymethylphenol (15.99 g) obtained in Example 21 was dissolved in anhydrous tetrahydrofuran (20 ml), the solution was added to commercially available magnesium powder (1.97 g) under argon, and a drop of an iodine solution in anhydrous tetrahydrofuran was added to the solution to start the reaction. When magnesium disappeared and the temperature of the reaction mixture returned to room temperature, commercially available tri-n-butylin chloride (23.99 g) dissolved in tetrahydrofuran (10 ml) was added slowly dropwise. The reaction mixture was stirred at room temperature for 4 hours and then partitioned between 5% aqueous ammonium chloride and chloroform. The chloroform layer was dried with anhydrous magnesium sulfate and the solvent was then removed by reduced-pressure distillation to obtain 31.39 g of the title compound (yield: 100%).

15

¹H-NMR (CDCl₃, 90MHz) : δ 0.80~1.65 (m, 27H), 3.48 (s, 3H), 5.17 (s, 2H), 6.91~7.42 (m, 4H)
 Mass spectrometry data (FD-MS, m/z) : 428 (M⁺+1)

20 Example 23 (Reference Example)

4-Hydroxyphenyl 4-trifluoromethylphenyl ketone

4-Tri-n-butylin-1-methoxymethylphenol (1.282 g) obtained in Example 22 and commercially available 4-(trifluoromethyl)benzoyl chloride (626 mg) were dissolved in chloroform (5 ml), commercially available bis(triphenylphosphine)palladium (II) chloride (8 mg) was added, and the admixture was refluxed for 5 hours. The reaction mixture was partitioned between water and ether, the ether layer was washed with saturated aqueous potassium fluoride, and the ether layer obtained by partitioning with brine was dried with anhydrous magnesium sulfate. The residue (1.028 g) obtained by removing the solvent by reduced-pressure distillation was dissolved in tetrahydrofuran (2 ml), water (5 ml) and 6 N aqueous hydrochloric acid (12 ml) were added, and the admixture was refluxed for 4.5 hours. The resulting reaction mixture was partitioned between brine and ether, and the ether layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/acetone to obtain 348 mg of the title compound (yield: 30%).

35

Mass spectrometry data (FD-MS, m/z) : 266 (M⁺)

Example 24

(4-Trifluoromethylphenyl)[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]methanone [29]

40

4-Chloro-6,7-dimethoxyquinoline (81 mg) and 4-hydroxyphenyl 4-trifluoromethylphenyl ketone (288 mg) obtained in Example 23 were mixed and stirred at 180 °C for 20 minutes, and the reaction mixture was then purified by thin layer chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 98 mg of the title compound (yield: 60%).

45

¹H-NMR (CDCl₃, 500MHz) : δ 4.03 (s, 3H), 4.06 (s, 3H), 6.68 (d, J=4.9Hz, 1H), 7.29 (d, J=8.5Hz, 2H), 7.46 (s, 1H), 7.47 (s, 1H), 7.78 (d, J=7.9Hz, 2H), 7.91 (d, J=7.9Hz, 2H), 7.94 (d, J=9.2Hz, 2H), 8.59 (d, J=4.9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 453 (M⁺)

Example 25 (Reference Example)

50

4-Hydroxyphenyl 4-methylphenyl ketone

4-Tri-n-butylin-1-methoxymethylphenol (1.282 g) obtained in Example 22 and commercially available 4-toluoyl chloride (464 mg) were dissolved in chloroform (5 ml), commercially available bis(triphenylphosphine)palladium(II) chloride (8 mg) was added, and the admixture was refluxed for 8 hours. The reaction mixture was partitioned in the same manner as described in Example 23 and the resulting ether layer was dried with anhydrous magnesium sulfate. The residue (967 mg) obtained by removing the solvent by reduced-pressure distillation was dissolved in tetrahydrofuran (0.5 ml), water (4 ml) and 6 N aqueous hydrochloric acid (10 ml) were added, and the admixture was refluxed for

7 hours. The reaction mixture was treated in the same manner as described in Example 23 to obtain 271 mg of the title compound (yield: 34%).

5 Mass spectrometry data (FD-MS, m/z) : 212 (M⁺)

Example 26

[4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl](4-methylphenyl)methanone [30]

10 4-Chloro-6,7-dimethoxyquinoline (89 mg) and 4-hydroxyphenyl 4-methylphenyl ketone (248 mg) obtained in Example 25 were mixed and stirred at 180 °C for 10 minutes, and the reaction mixture was then purified in the same manner as described in Example 24 to obtain 118 mg of the title compound (yield: 74%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 2.45 (s, 3H), 4.03 (s, 3H), 4.06 (s, 3H), 6.65 (d, J=5.5Hz, 1H), 7.27 (d, J=8.6Hz, 2H), 7.30 (d, J=7.9Hz, 2H), 7.46 (s, 1H), 7.49 (s, 1H), 7.74 (d, J=7.9Hz, 2H), 7.91 (d, J=8.5Hz, 2H), 8.57 (d, J=4.9Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 399 (M⁺)

Example 27 (Reference Example)

20 3-Chlorophenyl 4-hydroxyphenyl ketone

25 4-Tri-n-butylin-1-methoxymethylphenol (1.282 g) obtained in Example 22 and commercially available 3-chlorobenzoyl chloride (525 mg) were dissolved in chloroform (5 ml), commercially available bis(triphenylphosphine)palladium(II) chloride (8 mg) was added, and the admixture was refluxed for 7 hours. The reaction mixture was partitioned in the same manner as described in Example 23, and the resulting ether layer was dried with anhydrous magnesium sulfate. A portion (1.563 g) of the residue (1.914 g) obtained by removing the solvent by reduced-pressure distillation was dissolved in tetrahydrofuran (1 ml), water (7 ml) and 6 N aqueous hydrochloric acid (17 ml) were added, and the admixture was refluxed for 8 hours. The reaction mixture was treated in the same manner as described in Example 23 to obtain 313 mg of the title compound (yield: 22%).

30 Mass spectrometry data (FD-MS, m/z) : 232 (M⁺)

Example 28

35 (3-Chlorophenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)methanone [31]

40 4-Chloro-6,7-dimethoxyquinoline (89 mg) and 3-chlorophenyl 4-hydroxyphenyl ketone (279 mg) obtained in Example 27 were mixed and stirred at 180 °C for 20 minutes. The reaction mixture was then purified in the same manner as described in Example 24 to obtain 67 mg of the title compound (yield: 40%).

45 ¹H-NMR (CDCl₃, 500MHz) : δ 4.05 (s, 3H), 4.01 (s, 3H), 6.71 (d, J=5.5Hz, 1H), 7.31 (d, J=8.5Hz, 2H), 7.51 (s, 1H), 7.69 (s, 1H), 7.94 (d, J=8.5Hz, 2H), 8.12 (s, 1H), 7.37~8.03 (m, 4H)

Mass spectrometry data (FD-MS, m/z) : 419 (M⁺)

45 Example 29 (Reference Example)

4-t-Butylphenyl 4-methoxyphenyl ketone

50 To commercially available nitromethane (5 ml) were added commercially available anisole (541 mg), commercially available 4-t-butylbenzoyl chloride (983 mg) and commercially available scandium(III) trifluoromethanesulfonate (492 mg), and the admixture was stirred at 60 °C for 21 hours. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/acetone to obtain 862 mg of the title compound (yield: 64%).

55 Mass spectrometry data (FD-MS, m/z) : 268 (M⁺)

Example 30 (Reference Example)

4-t-Butylphenyl 4-hydroxyphenyl ketone

5 4-t-Butylphenyl 4-methoxyphenyl ketone (862 mg) obtained in Example 29 was dissolved in N,N-dimethylformamide (35 ml), sodium thiomethoxide (562 mg) was added, and the admixture was refluxed for 3 hours under argon. The reaction mixture was partitioned between 10% aqueous phosphoric acid and ethyl acetate. The ethyl acetate layer was then dried with anhydrous magnesium sulfate and the solvent was removed by reduced-pressure distillation to obtain 794 mg of the title compound (yield: 97%).

10 ¹H-NMR (CDCl₃, 500MHz) : δ 1.36 (s, 9H), 6.92 (d, J=8.5Hz, 2H), 7.49 (d, J=8.6Hz, 2H), 7.72 (d, J=7.9Hz, 2H), 7.79 (d, J=8.5Hz, 2H)
 Mass spectrometry data (FD-MS, m/z) : 254 (M⁺)

15 Example 31

(4-t-Butylphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone [32]

20 4-Chloro-6,7-dimethoxyquinoline (341 mg) and 4-t-butylphenyl 4-hydroxyphenyl ketone (775 mg) obtained in Example 30 were mixed and stirred at 150 °C for 15 minutes. The reaction mixture was then purified by column chromatography on silica gel eluting with hexane/acetone to obtain 72 mg of the title compound (yield: 11%).

25 ¹H-NMR (CDCl₃, 500MHz) : δ 1.38 (s, 9H), 4.04 (s, 3H), 4.06 (s, 3H), 6.65 (d, J=5.5Hz, 1H), 7.27 (d, J=8.6Hz, 2H), 7.45 (s, 1H), 7.50 (s, 1H), 7.52 (d, J=8.5Hz, 2H), 7.78 (d, J=8.6Hz, 2H), 7.94 (d, J=8.6Hz, 2H), 8.57 (d, J=4.9Hz, 1H)
 Mass spectrometry data (FAB-MS, m/z) : 442 (M⁺⁺¹)

Example 32 (Reference Example)

4-Biphenyl 4-methoxyphenyl ketone

30 To commercially available nitromethane (50 ml) were added commercially available anisole (3.244 g), commercially available 4-phenylbenzoyl chloride (6.500 g) and commercially available ytterbium(III) trifluoromethanesulfonate (1.861 g), and the admixture was stirred at 60 °C for 24 hours. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, a portion (1.00 g) of the resulting residue (9.842 g) was purified by column chromatography on silica gel eluting with hexane/acetone to obtain 300 mg of the title compound (yield: 34%).

35 ¹H-NMR (CDCl₃, 500MHz) : δ 3.90 (s, 3H), 6.98 (d, J=8.5Hz, 2H), 7.40 (t, J=7.3Hz, 1H), 7.48 (t, J=7.3Hz, 2H), 7.65 (d, J=7.3Hz, 2H), 7.76 (d, J=8.6Hz, 2H), 7.85 (d, J=8.5Hz, 2H), 7.87 (d, J=9.2Hz, 2H)
 Mass spectrometry data (FD-MS, m/z) : 288 (M⁺)

Example 33 (Reference Example)

4-Biphenyl 4-hydroxyphenyl ketone

40 4-Biphenyl 4-methoxyphenyl ketone (267 mg) obtained in Example 32 was dissolved in N,N-dimethylformamide (20 ml), sodium thiomethoxide (162 mg) was added, and the admixture was refluxed under argon for 3 hours. The reaction mixture was partitioned between 10% aqueous phosphoric acid and ethyl acetate. The ethyl acetate layer was washed with 0.5 N aqueous silver nitrate and then dried with anhydrous magnesium sulfate, the solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 207 mg of the title compound (yield: 82%).

45 ¹H-NMR (CDCl₃, 500MHz) : δ 6.91 (d, J=8.5Hz, 2H), 7.43 (t, J=7.3Hz, 1H), 7.52 (dd, J=7.3Hz, 7.9Hz, 2H), 7.70 (d, J=8.5Hz, 2H), 7.75 (d, J=7.9Hz, 2H), 7.77 (d, J=7.9Hz, 2H), 7.83 (d, J=7.9Hz, 2H)
 Mass spectrometry data (FD-MS, m/z) : 274 (M⁺)

Example 34

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(4-biphenyl)methanone [33]

5 4-Chloro-6,7-dimethoxyquinoline (65 mg) and 4-biphenyl 4-hydroxyphenyl ketone (79 mg) obtained in Example 33
 were mixed and stirred at 180 °C for 30 minutes. The reaction mixture was purified by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (10/1) to obtain 50 mg of the title compound (yield: 37%).

10 ¹H-NMR (CDCl₃, 90MHz) : δ 4. 11 (s, 3H), 4. 14 (s, 3H), 6. 74 (d, J=5. 3Hz, 1H), 7. 30~8. 09 (m, 15H), 8. 65 (d, J=5. 3Hz, 1H)
 Mass spectrometry data (FAB-MS, m/z) : 462 (M⁺)

Example 35 (Reference Example)

15 4-Methoxyphenyl 2-naphthyl ketone

20 To commercially available nitromethane (10 ml) were added commercially available anisole (1.081 g), commercially available 2-naphthoyl chloride (1.906 g) and commercially available ytterbium(III) trifluoromethanesulfonate (620 mg), and the admixture was stirred at 60 °C for 8 hours. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 817 mg of the title compound (yield: 31%).

25 ¹H-NMR (CDCl₃, 500MHz) : δ 3. 89 (s, 3H), 6. 98 (d, J=9. 2Hz, 2H), 7. 53 (t, J=8. 6Hz, 1H), 7. 58 (t, J=9. 2Hz, 1H), 7. 86~7. 93 (m, 6H), 8. 21 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 262 (M⁺)

Example 36 (Reference Example)

30 4-Hydroxyphenyl 2-naphthyl ketone

35 4-Methoxyphenyl 2-naphthyl ketone (735 mg) obtained in Example 35 was dissolved in N,N-dimethylformamide (20 ml), sodium thiomethoxide (491 mg) was added, and the admixture was refluxed under argon for 5 hours. The reaction mixture was treated in the same manner as described in Example 33 to obtain 595 mg of the title compound (yield: 86%).

40 ¹H-NMR (CDCl₃, 500MHz) : δ 6. 93 (d, J=7. 6Hz, 2H), 7. 61 (t, J=7. 0Hz, 1H), 7. 67 (t, J=7. 3Hz, 1H), 7. 74 (d, J=8. 5Hz, 2H), 7. 78~7. 80 (m, 1H), 8. 02~8. 10 (m, 3H), 8. 25 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 248 (M⁺)

Example 37

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(2-naphthyl)methanone [34]

45 4-Chloro-6,7-dimethoxyquinoline (112 mg) and 4-hydroxyphenyl 2-naphthyl ketone (124 mg) obtained in Example 36 were mixed and stirred at 180 °C for 30 minutes. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and then the chloroform layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, a portion (50 mg) of the resulting residue (227 mg) was purified by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1) to obtain 11 mg of the title compound (yield: 23%).

50 ¹H-NMR (CDCl₃, 90MHz) : δ 4. 05 (s, 3H), 4. 07 (s, 3H), 6. 70 (d, J=5. 3Hz, 1H), 7. 35 (s, 1H), 7. 48~7. 90 (m, 5H), 7. 96~8. 05 (m, 6H), 8. 29 (s, 1H), 8. 60 (d, J=5. 3Hz, 1H)
 Mass spectrometry data (FAB-MS, m/z) : 436 (M⁺+1)

Example 38 (Reference Example)

4-Methoxyphenyl 2-thienyl ketone

5 To commercially available nitromethane (10 ml) were added commercially available anisole (1.081 g), commercially available 2-thienoyl chloride (1.466 g) and commercially available ytterbium(III) trifluoromethanesulfonate (620 mg), and the admixture was stirred at 60 °C for 8 hours. The reaction mixture was treated in the same manner as described in Example 35 to obtain 965 mg of the title compound (yield: 44%).

10 $^1\text{H-NMR}$ (CDCl_3 , 500MHz) : δ 3.89 (s, 3H), 6.98 (d, $J=8.5\text{Hz}$, 2H), 7.16 (dd, $J=3.7\text{Hz}$, 4.9Hz, 1H), 7.64 (d, $J=3.7\text{Hz}$, 1H), 7.68 (d, $J=4.9\text{Hz}$, 1H), 7.90 (d, $J=8.6\text{Hz}$, 2H)
 Mass spectrometry data (FD-MS, m/z) : 218 (M^+)

Example 39 (Reference Example)

4-Hydroxyphenyl 2-thienyl ketone

20 4-Methoxyphenyl 2-thienyl ketone (804 mg) obtained in Example 38 was dissolved in N,N-dimethylformamide (30 ml), sodium thiomethoxide (645 mg) was added, and the admixture was refluxed under argon for 5 hours. The reaction mixture was partitioned in the same manner as described in Example 33. The ethyl acetate layer was dried with anhydrous magnesium sulfate, the solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform to obtain 702 mg of the title compound (yield: 93%).

25 $^1\text{H-NMR}$ (CDCl_3 , 500MHz) : δ 6.84 (brs, 1H), 6.93 (d, $J=8.5\text{Hz}$, 2H), 7.14 (dd, $J=3.7\text{Hz}$, 4.9Hz, 1H), 7.64 (d, $J=3.7\text{Hz}$, 1H), 7.68 (d, $J=4.9\text{Hz}$, 1H), 7.83 (d, $J=8.5\text{Hz}$, 2H)
 Mass spectrometry data (FD-MS, m/z) : 204 (M^+)

Example 40

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(2-thienyl)methanone [36]

30 4-Chloro-6,7-dimethoxyquinoline (112 mg) and 4-hydroxyphenyl 2-thienyl ketone (102 mg) obtained in Example 39 were mixed and stirred at 160 °C for 40 minutes. The reaction mixture was purified in the same manner as described in Example 24 to obtain 34 mg of the title compound (yield: 17%).

35 $^1\text{H-NMR}$ (CDCl_3 , 500MHz) : δ 4.04 (s, 3H), 4.07 (s, 3H), 6.65 (d, $J=5.5\text{Hz}$, 1H), 7.20 (dd, $J=3.7\text{Hz}$, 4.9Hz, 1H), 7.29 (d, $J=8.5\text{Hz}$, 2H), 7.47 (s, 1H), 7.49 (s, 1H), 7.70 (d, $J=3.1\text{Hz}$, 1H), 7.75 (d, $J=4.9\text{Hz}$, 1H), 8.00 (d, $J=8.6\text{Hz}$, 2H), 8.58 (d, $J=5.5\text{Hz}$, 1H)
 Mass spectrometry data (FAB-MS, m/z) : 392 (M^++1)

40 Example 41

(4-Chlorophenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone [37]

45 4-Chloro-6,7-dimethoxyquinoline (112 mg) and commercially available 4-chlorophenyl 4-hydroxyphenyl ketone (349 mg) were mixed and stirred at 180 °C for 20 minutes. The reaction mixture was purified by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1) to obtain 26 mg of the title compound (yield: 12%).

50 $^1\text{H-NMR}$ (CDCl_3 , 90MHz) : δ 4.03 (s, 3H), 4.07 (s, 3H), 6.66 (d, $J=5.3\text{Hz}$, 1H), 7.19~7.34 (m, 2H), 7.44~7.56 (m, 4H), 7.71~7.99 (m, 4H), 8.58 (d, $J=5.3\text{Hz}$, 1H)
 Mass spectrometry data (FD-MS, m/z) : 419 (M^+)

Example 42

(4-fluorophenyl){4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}methanone [38]

55 4-Chloro-6,7-dimethoxyquinoline (112 mg) and commercially available 4-fluorophenyl 4-hydroxyphenyl ketone (324 mg) were mixed and stirred at 170 °C for 20 minutes. The reaction mixture was then purified in the same manner

as described in Example 41 to obtain 114 mg of the title compound (yield: 57%).

5 ¹H-NMR (CDCl₃, 500MHz) : δ 4.04 (s, 3H), 4.07 (s, 3H), 6.65 (d, J=5.5Hz, 1H), 7.18 (d, J=8.5Hz, 1H), 7.20 (d, J=8.5Hz, 1H), 7.27 (s, 1H), 7.28 (s, 1H), 7.47 (d, J=8.5Hz, 2H), 7.86 (d, J=8.5Hz, 1H), 7.88 (d, J=8.5Hz, 1H), 7.90 (d, J=8.5Hz, 2H), 8.58 (d, J=4.9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 403 (M⁺)

Example 43

10 {4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(phenyl)methanone [39]

4-Chloro-6,7-dimethoxyquinoline (91 mg) and commercially available 4-hydroxybenzophenone (243 mg) were mixed and stirred at 180 °C for 30 minutes. The reaction mixture was purified in the same manner as described in Example 31 to obtain 38 mg of the title compound (yield: 24%).

15 ¹H-NMR (CDCl₃, 90MHz) : δ 4.03 (s, 3H), 4.05 (s, 3H), 6.66 (d, J=5.3Hz, 1H), 7.31~7.99 (m, 11H), 8.57 (d, J=5.3Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 385 (M⁺)

20 Example 44 (Reference Example)

3,5-dimethoxy toluene

25 Commercially available orcinol (5.77 g) was dissolved in acetonitrile (200 ml), dimethyl sulfate (8.47 ml) and potassium carbonate (12.3 g) were added, and the admixture was refluxed for 2.5 hours. The reaction mixture was poured into ice water and partitioned with chloroform, and the chloroform layer was dried with anhydrous magnesium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5/1) to obtain 5.04 g of the title compound (yield: 82%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 2.30 (s, 3H), 3.76 (s, 6H), 6.30 (s, 1H), 6.37 (s, 2H)

Example 45 (Reference Example)

2,6-Dimethoxy-4-methylphenyl 4-methoxyphenyl ketone

35 3,5-Dimethoxy toluene (1.00 g) obtained in Example 44 was dissolved in anhydrous tetrahydrofuran (10 ml), commercially available 2.5 M n-butyllithium-hexane solution (2.90 ml) was added at -45 °C under nitrogen, and the admixture was stirred for 3 hours. Commercially available 4-methoxybenzoyl chloride (1.23 g) was dissolved in tetrahydrofuran (10 ml), and the resulting solution was added slowly to the admixture at -45 °C. The reaction mixture 40 was stirred at room temperature for 1 hour and then partitioned between water and chloroform. The chloroform layer was dried with anhydrous magnesium sulfate, the solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5/1) to obtain 384 mg of the title compound (yield: 20%).

45 ¹H-NMR (CDCl₃, 500MHz) : δ 2.40 (s, 3H), 3.69 (s, 6H), 3.85 (s, 3H), 6.43 (s, 2H), 6.89 (d, J=9.2Hz, 2H), 7.82 (d, J=9.2Hz, 2H)

Example 46 (Reference Example)

50 2,6-Dihydroxy-4-methylphenyl 4-hydroxyphenyl ketone

55 2,6-Dimethoxy-4-methylphenyl 4-methoxyphenyl ketone (321 mg) obtained in Example 45 was dissolved in anhydrous methylene chloride (10 ml), commercially available boron tribromide (349 ml) was added slowly while cooled in ice, and the admixture was stirred at room temperature overnight. The reaction mixture was poured into ice water and then partitioned with ethyl acetate. The ethyl acetate layer was washed with brine and then dried with anhydrous magnesium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 87 mg of the title compound (yield: 68%).

¹H-NMR (CDCl₃, 500MHz) : δ 2. 16 (s, 3H), 6. 16 (s, 2H), 6. 79 (d, J=8. 6Hz, 2H), 7. 56 (d, J=8. 5Hz, 2H)

Example 47

5 **(2,6-Dihydroxy-4-methylphenyl){4-[6,7-dimethoxy-4-quinolyl]oxy}phenyl)methanone [42]**

4-Chloro-6,7-dimethoxyquinoline (61 mg) and 2,6-dihydroxy-4-methylphenyl 4-hydroxyphenyl ketone (100 mg) obtained in Example 46 were dissolved in diethylene glycol dimethyl ether (0.5 ml), and the solution was stirred at 170 °C for 20 minutes. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was washed with brine and then dried with anhydrous magnesium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 32 mg of the title compound (yield: 27%).

¹H-NMR (DMSO, 500MHz) :

15 δ 2. 18 (s, 3H), 3. 90 (s, 3H), 3. 95 (s, 3H), 6. 20 (s, 2H) 6. 68 (d, J=4. 9Hz, 1H), 7. 32 (d, J=9. 2Hz, 2H), 7. 42 (s, 1H), 7. 43 (s, 1H), 7. 82 (d, J=8. 6Hz, 2H), 8. 54 (d, J=5. 5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 432 (M⁺+1)

Example 48 (Reference Examples)

20 **6,7-Dimethoxy-4-(4-nitrophenoxy)quinoline**

4-Chloro-6,7-dimethoxyquinoline (1.84 g) and commercially available 4-nitrophenol (3.42 g) was mixed and stirred at 170 °C for 50 minutes. After cooling to room temperature in air, aqueous sodium hydrogen carbonate was added to the reaction mixture, and the admixture was extracted 3 times with ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol to obtain 4.54 g of the title compound (yield: 89%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 01 (s, 3H), 4. 06 (s, 3H), 6. 69 (d, J=4. 9Hz, 1H), 7. 27 (d, J=9. 1Hz, 2H), 7. 37 (s, 1H), 7. 47 (s, 1H), 8. 32 (d, J=9. 1Hz, 2H), 8. 62 (d, J=4. 9Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 326 (M⁺)

Example 49 (Reference Example)

35 **6,7-Dimethoxy-4-(4-aminophenoxy)quinoline**

6,7-Dimethoxy-4-(4-nitrophenoxy)quinoline (1.00 g) was dissolved in N,N-dimethylformamide/ethyl acetate (30 ml/15 ml), 10% palladium hydroxide-carbon (69 mg) was added, and the admixture was stirred at room temperature under hydrogen for 17 hours. The reaction mixture was filtered using Celite. The filtrate was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation to obtain 799 mg of the title compound (yield: 88%).

45 ¹H-NMR (CD₃OD, 500MHz) : δ 4. 00 (s, 3H), 4. 00 (s, 3H), 6. 47 (d, J=5. 5Hz, 1H), 6. 82 (d, J=8. 6Hz, 2H), 6. 96 (d, J=9. 2Hz, 2H), 7. 32 (s, 1H), 7. 62 (s, 1H), 8. 36 (d, J=5. 5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 296 (M⁺)

Example 50

50 **N-[4-[6,7-Dimethoxy-4-quinoliny]oxy]phenyl]-3-pyridinecarboxamide [61]**

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (57 mg) and commercially available nicotinic acid (37 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (79 mg) was added, and the admixture was stirred at room temperature for 5 hours. The reaction mixture was partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting crystallized product was washed with ether to obtain 47 mg of the title compound (yield: 61%).

⁵ ¹H-NMR (CDCl₃, 500MHz) : δ 4.05 (s, 3H), 4.06 (s, 3H), 6.49 (d, J=4.9Hz, 1H), 7.22 (d, J=8.6Hz, 2H), 7.42 (s, 1H), 7.47 (dd, J=4.9, 7.9Hz, 1H), 7.56 (s, 1H), 7.77 (d, J=9.2Hz, 1H), 8.26 (d, J=8.5Hz, 2H), 8.49 (d, J=4.9Hz, 1H), 8.79 (d, J=3.7Hz, 1H), 9.13 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 401 (M⁺)

¹⁰ Example 51

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-3,4-dimethoxyphenyl]carboxamide [62]

¹⁵ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (56 mg) and commercially available 3,4-dimethoxybenzoic acid (60 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (81 mg) was added, and the admixture was stirred at room temperature for 22 hours. The reaction mixture was partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting chloroform/acetone (10/1) to obtain 7 mg of the title compound (yield: 8%).

²⁰ ¹H-NMR (CDCl₃, 500MHz) : δ 3.87 (s, 3H), 3.87 (s, 3H), 4.06 (s, 3H), 4.07 (s, 3H), 6.48 (d, J=5.5Hz, 1H), 6.63 (d, J=8.5Hz, 2H), 7.18 (d, J=9.2Hz, 2H), 7.34 (m, 2H), 7.43 (s, 1H), 7.55 (s, 1H), 7.57 (s, 1H), 7.76 (d, J=8.6Hz, 2H), 8.48 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 460 (M⁺)

Example 52

²⁵ N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-cyclohexanecarboxamide [63]

³⁰ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) and commercially available cyclohexanecarboxylic acid (46 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (84 mg) was added, and the admixture was stirred at room temperature for 22 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 45 mg of the title compound (yield: 64%).

³⁵ ¹H-NMR (CDCl₃, 500MHz) : δ 1.30 (m, 2H), 1.56 (m, 2H), 1.73 (m, 2H), 1.85 (m, 2H), 1.97 (m, 2H), 2.26 (m, 1H), 4.05 (s, 3H), 4.05 (s, 3H), 6.43 (d, J=5.5Hz, 1H), 7.14 (d, J=8.5Hz, 2H), 7.36 (s, 1H), 7.42 (s, 1H), 7.55 (s, 1H), 7.63 (d, J=8.5Hz, 2H), 8.47 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 406 (M⁺)

Example 53

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-2-furancarboxamide [64]

⁴⁰ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (55 mg) and commercially available 2-furancarboxylic acid (32 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (91 mg) was added, and the admixture was stirred at room temperature for 22 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 35 mg of the title compound (yield: 48%).

⁴⁵ ¹H-NMR (CDCl₃, 500MHz) : δ 4.04 (s, 3H), 4.05 (s, 3H), 6.49 (d, J=4.9Hz, 1H), 6.57 (dd, J=1.8, 8.7Hz, 1H), 7.20 (d, J=8.6Hz, 2H), 7.28 (d, J=7.9Hz, 1H), 7.42 (s, 1H), 7.51 (s, 1H), 7.56 (s, 1H), 7.77 (d, J=9.2Hz, 2H), 8.35 (s, 1H), 8.49 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 390 (M⁺)

⁵⁰ Example 54

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-3-thiophenecarboxamide [65]

⁵⁵ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) and commercially available 3-thiophenecarboxylic acid (44 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (82 mg) was added, and the admixture was stirred at room temperature for 31 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 41 mg of the title compound (yield: 55%).

¹H-NMR (CDCl₃, 500MHz) : δ 4.02 (s, 3H), 4.04 (s, 3H), 6.46 (d, J=5.5Hz, 1H), 7.17 (d, J=8.6Hz, 2H), 7.38 (m, 1H), 7.55 (d, J=1.2Hz, 1H), 7.56 (s, 1H), 7.73 (d, J=8.6Hz, 2H), 8.05 (dd, J=1.2, 3.1Hz, 1H), 8.37 (s, 1H), 8.47 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 406 (M⁺)

5

Example 55

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-(4-nitrophenyl)carboxamide [66]

¹⁰ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (110 mg) and commercially available 4-nitrobenzoic acid (100 mg) were dissolved in N,N-dimethylformamide (4 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (176 mg) was added, and the admixture was stirred at room temperature for 22 hours. The reaction mixture was then purified in the same manner as described in Example 50 to obtain 126 mg of the title compound (yield: 77%).

¹⁵ ¹H-NMR (DMSO-d₆, 500MHz) : δ 3.94 (s, 3H), 3.95 (s, 3H), 6.49 (d, J=5.5Hz, 1H), 7.29 (d, J=9.2Hz, 2H), 7.39 (s, 1H), 7.52 (s, 1H), 7.93 (d, J=9.2Hz, 2H), 8.21 (d, J=8.6Hz, 2H), 8.39 (d, J=9.2Hz, 2H), 8.48 (d, J=5.5Hz, 1H), 10.7 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 445 (M⁺)

20 Example 56

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-(N,N-dimethylaminophenyl)carboxamide [67]

²⁵ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) and commercially available 4-(dimethylamino)benzoic acid (44 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (83 mg) was added, and the admixture was stirred at room temperature for 16 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 7 mg of the title compound (yield: 10%).

³⁰ ¹H-NMR (CDCl₃, 500MHz) : δ 3.06 (s, 6H), 4.05 (s, 3H), 4.06 (s, 3H), 6.48 (d, J=4.9Hz, 1H), 6.71 (d, J=8.6Hz, 2H), 7.17 (d, J=8.5Hz, 2H), 7.44 (s, 1H), 7.57 (s, 1H), 7.74 (d, J=8.5Hz, 2H), 7.81 (d, J=9.2Hz, 2H), 7.94 (s, 1H), 8.49 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 443 (M⁺)

Example 57

35

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-(4-acetylphenyl)carboxamide [68]

⁴⁰ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) and commercially available 4-acetylbenzoic acid (46 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (87 mg) was added, and the admixture was stirred at room temperature for 22 hours. The reaction mixture was then purified in the same manner as described in Example 50 to obtain 43 mg of the title compound (yield: 53%).

⁴⁵ ¹H-NMR (DMSO-d₆, 500MHz) : δ 2.66 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.48 (d, J=4.9Hz, 1H), 7.28 (d, J=9.2Hz, 2H), 7.39 (s, 1H), 7.52 (s, 1H), 7.94 (d, J=9.2Hz, 2H), 8.10 (m, 4H), 8.48 (d, J=5.5Hz, 1H), 10.6 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 442 (M⁺)

Example 58

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-(4-butylphenyl)carboxamide [69]

50

⁵⁵ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) and commercially available 4-butyl benzoate (54 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (85 mg) was added, and the admixture was stirred at room temperature for 22 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 65 mg of the title compound (yield: 78%).

¹H-NMR (CDCl₃, 500MHz) : δ 0.95 (t, J=7.3Hz, 3H), 1.38 (m, 2H), 1.64 (m, 2H), 2.69 (t, J=8.0Hz, 2H), 4.05 (s, 3H), 4.06 (s, 3H), 6.48 (d, J=5.5Hz, 1H), 7.19 (d, J=9.2Hz, 2H), 7.30 (d, J=8.6Hz, 2H), 7.42 (s, 1H), 7.57 (s, 1H), 7.75 (d, J=8.6Hz, 2H), 7.82 (d, J=8.6Hz, 2H), 8.03 (s, 1H), 8.49 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 456 (M⁺)

Example 59

5 N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-4-aminophenyl]carboxamide [70]

10 {4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-4-nitrophenyl}carboxamide (100 mg) was dissolved in N,N-dimethylformamide/ethyl acetate (9 ml/5 ml), 10% palladium-carbon (69 mg) was added, and the admixture was stirred at room temperature under hydrogen for 22 hours. The reaction mixture was filtered using Celite. The filtrate was then distilled under reduced pressure to remove the solvents, and the resultant residue was purified by column chromatography on silica gel eluting chloroform/acetone to obtain 85 mg of the title compound (yield: 91%).

15 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 5. 75 (brs, 2H), 6. 46 (d, J=4. 9Hz, 1H), 6. 61 (d, J=8. 6Hz, 2H), 7. 22 (d, J=9. 2Hz, 2H), 7. 39 (s, 1H), 7. 52 (s, 1H), 7. 73 (d, J=8. 5Hz, 2H), 7. 89 (d, J=9. 2Hz, 2H), 8. 46 (d, J=5. 5Hz, 1H), 9. 90 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 415 (M⁺)

Example 60

20 N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-4-pyridinecarboxamide [71]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) and commercially available isonicotinic acid (45 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (98 mg) was added, and the admixture was stirred at room temperature for 62 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 22 mg of the title compound (yield: 31%).

30 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 96 (s, 3H), 6. 48 (d, J=5. 5Hz, 1H), 7. 29 (d, J=9. 2Hz, 2H), 7. 39 (s, 1H), 7. 52 (s, 1H), 7. 88 (d, J=4. 3Hz, 2H), 7. 92 (d, J=8. 5Hz, 2H), 8. 48 (d, J=4. 9Hz, 1H), 8. 80 (d, J=4. 3Hz, 2H), 10. 6 (s, 1H)

35 Mass spectrometry data (FD-MS, m/z) : 401 (M⁺)

Example 61

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-2-thiophenecarboxamide [72]

35 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) and commercially available 2-thiophenecarboxylic acid (46 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (99 mg) was added, and the admixture was stirred at room temperature for 62 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 37 mg of the title compound (yield: 54%).

40 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 02 (s, 3H), 4. 04 (s, 3H), 6. 46 (d, J=5. 5Hz, 1H), 7. 11 (m, 1H), 7. 17 (d, J=8. 6Hz, 2H), 7. 40 (s, 1H), 7. 55 (m, 1H), 7. 56 (s, 1H), 7. 73 (d, J=8. 5Hz, 2H), 7. 73 (m, 1H), 8. 38 (s, 1H), 8. 48 (d, J=4. 9Hz, 1H)

45 Mass spectrometry data (FD-MS, m/z) : 406 (M⁺)

Example 62

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-4-biphenylcarboxamide [73]

50 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was suspended in triethylamine/methylene chloride (3 ml/2 ml), commercially available biphenylcarbonyl chloride (80 mg) was added, and the admixture was stirred at room temperature for 25 hours. Aqueous sodium hydrogen carbonate was added to the reaction mixture, and the resulting admixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone and further by washing resulting crystals with acetone to obtain 9 mg of the title compound (yield: 10%).

55 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 95 (s, 3H), 3. 95 (s, 3H), 6. 48 (d, J=5. 5Hz, 1H), 7. 28 (d, J=9. 2Hz, 2H), 7. 40

(s, 1H), 7.43 (t, J=7.3Hz, 1H), 7.50~7.53 (m, 3H), 7.77 (d, J=7.3Hz, 2H), 7.85 (d, J=8.6Hz, 2H), 7.96 (m, 2H), 8.08 (d, J=8.5Hz, 2H), 8.48 (d, J=4.9Hz, 1H), 10.4 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 476 (M⁺)

5 Example 63

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-4-butoxyphenyl]carboxamide [74]

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was suspended in triethylamine/methylene chloride (3 ml/2 ml), commercially available 4-butoxybenzoyl chloride (0.07 ml) was added, and the admixture was stirred at room temperature for 30 hours. The reaction mixture was then purified in the same manner as described in Example 62 to obtain 34 mg of the title compound (yield: 41%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 0.99 (t, J=7.3Hz, 3H), 1.52 (m, 2H), 1.80 (m, 2H), 4.03 (m, 2H), 4.04 (s, 3H), 4.05 (s, 3H), 6.47 (d, J=4.9Hz, 1H), 6.95 (d, J=9.2Hz, 2H), 7.18 (d, J=9.2Hz, 2H), 7.46 (s, 1H), 7.57 (s, 1H), 7.74 (d, J=9.2Hz, 2H), 7.86 (d, J=9.2Hz, 2H), 8.10 (s, 1H), 8.49 (d, J=4.9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 472 (M⁺)

Example 64

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-4-bromophenyl]carboxamide [75]

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) and commercially available 4-bromobenzoic acid (78 mg) were dissolved in N,N-dimethylformamide (2 ml). 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (102 mg) was added, and the admixture was stirred at room temperature for 17 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 43 mg of the title compound (yield: 52%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 4.07 (s, 3H), 4.07 (s, 3H), 6.53 (d, J=5.5Hz, 1H), 7.22 (d, J=9.2Hz, 2H), 7.37 (s, 1H), 7.50 (s, 1H), 7.62 (s, 1H), 7.65 (d, J=8.6Hz, 2H), 7.84 (d, J=8.6Hz, 2H), 7.86 (d, J=8.6Hz, 2H), 8.41 (d, J=5.5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 478 (M⁺), 480 (M⁺+2)

Example 65

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-4-methoxycarbonylphenyl]carboxamide [76]

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (100 mg) and commercially available monomethylterephthalic acid (130 mg) were dissolved in N,N-dimethylformamide (4 ml). 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (227 mg) was added, and the admixture was stirred at room temperature for 18 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 99 mg of the title compound (yield: 64%).

45 ¹H-NMR (CDCl₃, 500MHz) : δ 3.98 (s, 3H), 4.06 (s, 3H), 4.06 (s, 3H), 6.49 (d, J=4.9Hz, 1H), 7.22 (d, J=9.2Hz, 2H), 7.43 (s, 1H), 7.56 (s, 1H), 7.76 (d, J=9.2Hz, 2H), 7.97 (d, J=8.6Hz, 2H), 8.18 (d, J=8.6Hz, 2H), 8.49 (d, J=5.5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 458 (M⁺)

Example 66

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-2-pyridinecarboxamide [77]

50 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) and commercially available picolinic acid (42 mg) were dissolved in N,N-dimethylformamide (2 ml). 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (123 mg) was added, and the admixture was stirred at room temperature for 19 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 38 mg of the title compound (yield: 56%).

55 ¹H-NMR (CDCl₃, 500MHz) : δ 4.06 (s, 3H), 4.06 (s, 3H), 6.49 (d, J=5.5Hz, 1H), 7.23 (d, J=8.6Hz, 2H), 7.43 (s, 1H), 7.51 (m, 1H), 7.58 (s, 1H), 7.89 (d, J=9.2Hz, 2H), 7.94 (m, 1H), 8.33 (d, J=8.0Hz, 1H), 8.50 (d, J=5.5Hz, 1H), 8.64 (dd, J=1.8, 4.9Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 401 (M⁺)

Example 67

5 N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-(4-hydroxycarbonylphenyl)carboxamide [78]

10 {4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-(4-methoxycarbonylphenyl)carboxamide was dissolved in methanol (3 ml), 33% aqueous potassium hydroxide (1.5 ml) was added, and the admixture was stirred at room temperature for 2 hours. The reaction mixture was washed 2 times with ethyl acetate, and the water layer was neutralized with dilute hydrochloric acid and extracted 2 times with chloroform. The chloroform layer was dried with sodium sulfate, and the solvent was then removed by reduced-pressure distillation to obtain 34 mg of the title compound (yield: 45%).

15 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 93 (s, 3H), 3. 94 (s, 3H), 6. 47 (d, J=5. 5Hz, 1H), 7. 28 (d, J=9. 2Hz, 2H), 7. 39 (s, 1H), 7. 51 (s, 1H), 7. 92 (d, J=9. 2Hz, 2H), 8. 07 (m, 4H), 8. 47 (d, J=5. 5Hz, 1H), 10. 5 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 444 (M⁺)

Example 68

20 N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]cyclopentanecarboxamide [79]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) and commercially available cyclopentanecarboxylic acid (66 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (110 mg) was added, and the admixture was stirred at room temperature for 17 hours. The reaction mixture was purified in the same manner as described in Example 51 to obtain 35 mg of the title compound (yield: 50%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 64 (m, 2H), 1. 81 (m, 2H), 1. 91 (m, 4H), 2. 75 (m, 1H), 4. 04 (s, 3H), 4. 04 (s, 3H), 6. 44 (d, J=4. 9Hz, 1H), 7. 13 (d, J=9. 2Hz, 2H), 7. 45 (s, 1H), 7. 55 (m, 1H), 7. 65 (d, J=8. 6Hz, 2H), 8. 47 (d, J=5. 5Hz, 1H),
Mass spectrometry data (FD-MS, m/z) : 392 (M⁺)

35 Example 69

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]adamantanecarboxamide [81]

40 35 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) and commercially available adamantanecarboxylic acid (110 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (107 mg) was added, and the admixture was stirred at room temperature for 15 hours. The reaction mixture was purified in the same manner as described in Example 51 to obtain 13 mg of the title compound (yield: 17%).

45 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 82 (m, 6H), 2. 00 (m, 6H), 2. 13 (m, 3H), 4. 05 (s, 3H), 4. 05 (s, 3H), 6. 44 (d, J=4. 9Hz, 1H), 7. 15 (d, J=9. 2Hz, 2H), 7. 42 (s, 1H), 7. 55 (m, 1H), 7. 64 (d, J=9. 2Hz, 2H), 8. 46 (d, J=4. 9Hz, 1H),
Mass spectrometry data (FD-MS, m/z) : 458 (M⁺)

Example 70

45 N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-(4-acetoxyphenyl)carboxamide [80]

50 50 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (110 mg) and commercially available 4-acetoxybenzoic acid (207 mg) were dissolved in N,N-dimethylformamide (6 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (223 mg) was added, and the admixture was stirred at room temperature for 7 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 123 mg of the title compound (yield: 72%).

55 ¹H-NMR (CDCl₃, 500MHz) : δ 2. 35 (s, 3H), 4. 06 (s, 3H), 4. 06 (s, 3H), 6. 49 (d, J=4. 9Hz, 1H), 7. 21 (d, J=9. 2Hz, 2H), 7. 25 (d, J=9. 1Hz, 2H), 7. 43 (s, 1H), 7. 56 (s, 1H), 7. 73 (d, J=9. 2Hz, 2H), 7. 87 (s, 1H), 7. 93 (d, J=8. 6Hz, 2H), 8. 50 (d, J=5. 5Hz, 1H),
Mass spectrometry data (FD-MS, m/z) : 458 (M⁺)

Example 71

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-2-(6-acetoxynaphthyl)carboxamide [82]

5 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) and commercially available 6-acetoxy-2-naphthoic acid (121 mg) were dissolved in N,N-dimethylformamide (2 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (124 mg) was added, and the admixture was stirred at room temperature for 13 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 66 mg of the title compound (yield: 75%).

10 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 2. 38 (s, 3H), 4. 03 (s, 3H), 4. 05 (s, 3H), 6. 49 (d, J=5. 5Hz, 1H), 7. 20 (d, J=9. 2Hz, 2H), 7. 30 (dd, J=2. 4, 9. 2Hz, 1H), 7. 42 (s, 1H), 7. 57 (m, 1H), 7. 61 (d, J=1. 8Hz, 1H), 7. 81 (d, J=9. 2Hz, 2H), 7. 86 (d, J=8. 6Hz, 1H), 7. 89 (d, J=9. 2Hz, 1H), 7. 94 (d, J=8. 6Hz, 1H), 8. 38 (s, 1H), 8. 49 (d, J=4. 9Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 508 (M⁺)

15 Example 72

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-4-hydroxyphenyl]carboxamide [83]

20 N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-4-acetoxyphenyl]carboxamide (103 mg) was dissolved in methanol (4 ml), 35% aqueous potassium hydroxide (2 ml) was added, and the admixture was stirred at room temperature for 5 hours. The reaction mixture was partitioned with ethyl acetate/water, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting crystals were washed with ether to obtain 77 mg of the title compound (yield: 82%).

25 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 46 (d, J=4. 9Hz, 1H), 6. 87 (d, J=8. 5Hz, 2H), 7. 24 (d, J=9. 2Hz, 2H), 7. 39 (s, 1H), 7. 52 (s, 1H), 7. 87 (d, J=8. 6Hz, 2H), 7. 90 (d, J=9. 2Hz, 2H), 8. 47 (d, J=5. 5Hz, 1H), 10. 1 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 417 (M⁺+1)

30 Example 73

N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-2-(6-hydroxynaphthyl)carboxamide [84]

35 N-[4-[(6,7-Dimethoxy-4-quinolinyloxy)phenyl]-2-(6-acetoxynaphthyl)carboxamide (47 mg) was dissolved in methanol (4 ml), 35% aqueous potassium hydroxide (2 ml) was added, and the admixture was stirred at room temperature for 5 hours. The reaction mixture was then purified in the same manner as described in the Example 72 to obtain 37 mg of the title compound (yield: 86%).

40 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3. 95 (s, 3H), 3. 95 (s, 3H), 6. 49 (d, J=4. 9Hz, 1H), 7. 18 (m, 1H), 7. 20 (s, 1H), 7. 27 (d, J=8. 6Hz, 2H), 7. 39 (s, 1H), 7. 53 (s, 1H), 7. 80 (d, J=8. 5Hz, 1H), 7. 92~7. 98 (m, 4H), 8. 47~8. 48 (m, 2H), 10. 0 (brs, 1H), 10. 4 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 467 (M⁺+1)

Example 74

N - (4 - M e t h o x y p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
q u i n o l i n y l) o x y] p h e n y l] u r e a [4 3]

50

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) was dissolved in toluene (3 ml) with heat, 4-methoxyphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 30 minutes. The separated crystals were filtered and washed with toluene to obtain 54 mg of the title compound (yield: 68%).

55

$^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3. 72 (s, 3H), 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 44 (d, J=4. 9Hz, 1H), 6. 87 (d, J=8. 5Hz, 2H), 7. 19 (d, J=9. 2Hz, 2H), 7. 37 (d, J=8. 5Hz, 2H), 7. 38 (s, 1H), 7. 52 (s, 1H), 7. 58 (d, J=8. 5Hz, 2H), 8. 46 (d, J=5. 5Hz, 1H), 8. 50 (s, 1H), 8. 73 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 445 (M⁺)

Example 75

5 N - (4 - F l u o r o p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
q u i n o l i n y l) o x y] p h e n y l } u r e a [4 4]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) was dissolved in toluene (3 ml) with heat, 4-fluorophenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 70 minutes. The separated crystals were filtered and washed with toluene to obtain 38 mg of the title compound (yield: 48%).

15 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 44 (d, J=4. 9Hz, 1H), 7. 12 (m, 2H), 7. 19 (m, 2H),
 7. 38 (s, 1H), 7. 47 (m, 2H), 7. 51 (s, 1H), 7. 59 (d, J=9. 2Hz, 2H), 8. 45 (d, J=5. 5Hz, 1H), 8. 72 (s, 1H), 8. 79 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 433 (M⁺)

Example 76

20 N - (4 - B r o m o p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
q u i n o l i n y l) o x y] p h e n y l } u r e a [4 5]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (3 ml) with heat, 4-bromophenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 50 minutes. The separated crystals were filtered and washed with toluene to obtain 56 mg of the title compound (yield: 64%).

30 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 44 (d, J=5. 5Hz, 1H), 7. 19 (d, J=9. 2Hz, 2H), 7. 39
 (s, 1H), 7. 45 (m, 4H), 7. 51 (s, 1H), 7. 59 (d, J=9. 2Hz, 2H), 8. 46 (d, J=5. 5Hz, 1H), 8. 86 (s, 1H), 8. 86 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 493 (M⁺), 495 (M⁺+2)

Example 77

35 N - { 4 - [(6 , 7 - D i m e t h o x y - 4 - q u i n o l i n y l) o x y] p h e n y l } - N ' - (4 -
n i t r o p h e n y l) u r e a [4 6]

40 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (103 mg) was dissolved in toluene (10 ml) with heat, 4-nitrophenyl isocyanate (366 mg) was added, and the admixture was refluxed with heat for 60 minutes. The separated crystals were filtered and washed with toluene to obtain 141 mg of the title compound (yield: 88%).

45 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 45 (d, J=5. 5Hz, 1H), 7. 23 (d, J=8. 6Hz, 2H), 7. 39
 (s, 1H), 7. 51 (s, 1H), 7. 62 (d, J=9. 2Hz, 2H), 7. 71 (d, J=9. 2Hz, 2H), 8. 20 (d, J=9. 2Hz, 2H), 8. 46 (d, J=5. 5Hz,
 1H), 9. 08 (s, 1H), 9. 49 (s, 1H)
 50 Mass spectrometry data (FD-MS, m/z) : 460 (M⁺)

Example 78

5 N - (4 - B u t y l p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
quinolinyl)oxy]phenyl}urea [47]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (3 ml) with heat, 4-butylphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 26 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 36 mg of the title compound (yield: 45%).

15 ¹H-NMR (CDCl₃/CD₃OD, 500MHz) : δ 0. 93 (m, 3H), 1. 35 (m, 2H), 1. 57 (m, 2H), 2. 57 (m, 2H), 4. 06 (s, 3H), 4. 06 (s, 3H), 6. 49 (m, 1H), 7. 14 (m, 4H), 7. 33~7. 62 (m, 6H), 8. 39 (m, 1H)
Mass spectrometry data (FD-MS, m/z) : 471 (M⁺)

Example 79

20 N - (4 - a m i n o p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
quinolinyl)oxy]phenyl}urea [48]

25 N-[{6,7-Dimethoxy-4-quinolinyl}oxy]phenyl]-N'-(4-nitro)phenylurea (111 mg) was dissolved in N,N-dimethylformamide (7 ml), 10% palladium hydroxide-carbon (100 mg) was added, and the admixture was stirred at room temperature under hydrogen for 22 hours. The reaction mixture was filtered using Celite. The filtrate was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation to obtain 66 mg of the title compound (yield: 63%).

30 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 94 (s, 3H), 4. 74 (brs, 2H), 6. 43 (d, J=4. 9Hz, 1H), 6. 52 (d, J=8. 6Hz, 2H), 7. 08 (d, J=8. 6Hz, 2H), 7. 16 (d, J=9. 2Hz, 2H), 7. 38 (s, 1H), 7. 51 (s, 1H), 7. 55 (d, J=9. 2Hz, 2H), 8. 14 (s, 1H), 8. 45 (d, J=4. 9Hz, 1H), 8. 61 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 430 (M⁺)

Example 80

35 N - (4 - A c e t y l p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
quinolinyl)oxy]phenyl}urea [49]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (3 ml) with heat, 4-acetylphenyl isocyanate (210 mg) was added, and the admixture was refluxed with heat for 20 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 50 mg of the title compound (yield: 64%).

50 ¹H-NMR (CDCl₃/CD₃OD, 500MHz) : δ 2. 59 (s, 3H), 4. 07 (s, 3H), 4. 07 (s, 3H), 6. 50 (d, J=5. 5Hz, 1H), 7. 17 (d, J=8. 5Hz, 2H), 7. 36 (s, 1H), 7. 58 (s, 1H), 7. 58 (d, J=8. 5Hz, 2H), 7. 60 (d, J=8. 5Hz, 2H), 7. 94 (d, J=8. 5Hz, 2H), 8. 40 (d, J=5. 5Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 457 (M⁺)

Example 81

5 N-[4-[(6,7-Dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-
phenoxyphenyl)urea [50]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) was dissolved in toluene (3 ml) with heat, 4-phenoxyphenyl
isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 30 minutes. The resulting residue was puri-
fied by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 55 mg of the title com-
pound (yield: 60%).

15 ¹H-NMR (CDCl₃/CD₃OD, 500MHz) : δ 4.46 (s, 3H), 4.46 (s, 3H), 6.51 (m, 1H), 6.98~7.62 (m, 15H), 8.40 (m, 1H)
Mass spectrometry data (FD-MS, m/z) : 507 (M⁺)

15 Example 82

20 N-(4-Isopropylphenyl)-N'-(4-[(6,7-dimethoxy-4-
quinolinyl)oxy]phenyl)urea [51]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (3 ml) with heat, 4-isopropylphenyl
isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 26 minutes. The resulting residue was puri-
fied by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 70 mg of the title com-
pound (yield: 90%).

30 ¹H-NMR (CD₃OD, 500MHz) : δ 1.18 (d, J=6.7Hz, 6H), 2.82 (m, 1H), 3.97 (s, 3H), 4.01 (s, 3H), 6.37 (d, J=5.5Hz,
1H), 7.04 (d, J=8.5Hz, 2H), 7.11 (d, J=8.5Hz, 2H), 7.25 (d, J=8.5Hz, 2H), 7.26 (s, 1H), 7.38 (s, 1H), 7.41 (d,
J=9.2Hz, 2H), 7.54 (s, 1H), 7.82 (s, 1H), 8.03 (s, 1H), 8.42 (d, J=5.5Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 457 (M⁺)

35 Example 83

40 N-(4-Trifluoromethylphenyl)-N'-(4-[(6,7-dimethoxy-4-
quinolinyl)oxy]phenyl)urea [52]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) was dissolved in toluene (3 ml) with heat, 4-trifluoromethyl-
phenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 10 minutes. The separated crystals
were filtered and washed with toluene to obtain 77 mg of the title compound (yield: 88%).

50 ¹H-NMR (CDCl₃, 500MHz) : δ 4.05 (s, 3H), 4.05 (s, 3H), 6.52 (d, J=5.5Hz, 1H), 7.18 (d, J=9.2Hz, 2H), 7.36 (s,
1H), 7.56 (s, 1H), 7.59 (d, J=8.6Hz, 2H), 7.62 (d, J=8.6Hz, 2H), 7.63 (s, 1H), 8.40 (d, J=5.5Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 483 (M⁺)

55 Example 84

55 N-(4-n-Butylphenyl)-N'-(4-[(6,7-dimethoxy-4-
quinolyl)oxy]phenyl)urea [147]

6,7-Dimethoxy-4-(2-aminophenoxy)quinoline (56 mg), which was obtained, analogously to Example 49, by reduc-

ing 6,7-dimethoxy-4-(2-nitrophenoxy)quinoline obtained in the same manner as described in Example 48, except that 2-nitrophenol was used in place of 4-nitrophenol, was dissolved in toluene (3 ml) with heat, 4-n-butylphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 30 minutes. The resulting residue was purified by chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 45 mg of the title compound (yield: 50%).

5

¹H-NMR (CDCl₃, 500MHz) : δ 0. 89 (t, J=7. 3Hz, 3H), 1. 30 (m, 2H), 1. 52 (m, 2H), 2. 50 (m, 2H), 3. 90 (s, 3H), 3. 93 (s, 3H), 6. 22 (d, J=4. 9Hz, 1H), 6. 87 (d, J=7. 3Hz, 1H), 6. 96~7. 01 (m, 4H), 7. 15 (brs, 1H), 7. 28~7. 31 (m, 4H), 8. 12 (brs, 1H), 8. 26 (d, J=4. 9Hz, 1H), 8. 58 (d, J=7. 9Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 471 (M⁺)

10

Example 85

15

N - (4 - n - B u t y l p h e n y l) - N ' - { 3 - [(6 , 7 - d i m e t h o x y - 4 -
quinolyl)oxy]phenyl}urea [91]

20

6,7-Dimethoxy-4-(3-aminophenoxy)quinoline (51 mg), which was obtained, analogously to Example 49, by reducing 6,7-dimethoxy-4-(3-nitrophenoxy)quinoline obtained in the same manner as described in Example 48, except that 3-nitrophenol was used in place of 4-nitrophenol, was dissolved in toluene (3 ml) with heat, 4-n-butylphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 50 minutes. The resulting residue was purified by chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 26 mg of the title compound (yield: 32%).

25

¹H-NMR (CDCl₃, 500MHz) : δ 0. 89 (t, J=7. 3Hz, 3H), 1. 30 (m, 2H), 1. 52 (m, 2H), 2. 51 (m, 2H), 3. 95 (s, 1H), 4. 00 (s, 1H), 6. 49 (d, J=5. 5Hz, 1H), 6. 81 (d, J=8. 0Hz, 1H), 7. 04 (d, J=7. 9Hz, 2H), 7. 21~7. 30 (m, 5H), 7. 37 (s, 1H), 7. 51 (s, 1H), 7. 84 (brs, 1H), 8. 24 (brs, 1H), 8. 43 (d, J=4. 9Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 471 (M⁺)

30

Example 86

N-n-Butyl-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea
[139]

35

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (3 ml) with heat, n-butyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 14 hours. The resulting residue was purified by chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 31 mg of the title compound (yield: 46%).

¹H-NMR (CDCl₃, 500MHz) : δ 0. 93 (t, J=7. 3Hz, 3H), 1. 37 (m, 2H), 1. 53 (m, 2H), 3. 28 (m, 2H), 4. 04 (s, 3H), 4. 04 (s, 3H), 5. 04 (brs, 1H), 6. 44 (d, J=5. 5Hz, 1H), 6. 98 (brs, 1H), 7. 11 (d, J=9. 2Hz, 2H), 7. 41 (s, 1H), 7. 43 (d, J=9. 2Hz, 2H), 7. 55 (s, 1H), 8. 46 (d, J=4. 9Hz, 1H)

45

Mass spectrometry data (FD-MS, m/z) : 395 (M⁺)

Example 87

N-[4-(6,7-Dimethoxy-4-quinolyl)oxy]phenyl]-4-trifluoromethylphenyl)carboxamide [157]

50

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) and commercially available 4-trifluoromethanebenzoic acid (102 mg) were dissolved in N,N-dimethylformamide (3 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (102 mg) was added, and the admixture was stirred at room temperature for 14 hours. The reaction mixture was partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting crystallized product was washed with ethyl acetate to obtain 32 mg of the title compound (yield: 38%).

¹H-NMR (CDCl₃, 500MHz) : δ 4. 04 (s, 3H), 4. 05 (s, 3H), 6. 48 (d, J=4. 9Hz, 1H), 7. 22 (d, J=8. 5Hz, 2H), 7. 41 (s,

1H), 7. 55 (s, 1H), 7. 76 (d, J=8. 5Hz, 2H), 7. 76 (d, J=8. 6Hz, 2H), 8. 02 (d, J=7. 9Hz, 2H), 8. 13 (brs, 1H), 8. 49 (d, J=5. 5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 468 (M⁺)

5 Example 88

N-[4-[6,7-Dimethoxy-4-quinolyl]oxy]phenyl]-[4-cyclohexylphenyl]carboxamide [158]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) and commercially available 4-cyclohexylbenzoic acid (109 mg) were dissolved in N,N-dimethylformamide (3 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (110 mg) was added, and the admixture was stirred at room temperature for 14 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 54 mg of the title compound (yield: 64%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 25~1. 86 (m, 10H), 2. 55 (m, 1H), 4. 01 (s, 3H), 4. 03 (s, 3H), 6. 46 (d, J=5. 5Hz, 1H), 7. 16 (d, J=8. 5Hz, 2H), 7. 27 (d, J=7. 9Hz, 2H), 7. 39 (s, 1H), 7. 55 (s, 1H), 7. 75 (d, J=9. 2Hz, 2H), 7. 83 (d, J=8. 6Hz, 2H), 8. 46 (d, J=5. 5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 482 (M⁺)

Example 89

20 N-[3-[6,7-Dimethoxy-4-quinolyl]oxy]phenyl]-[4-t-butylphenyl]carboxamide [159]

25 6,7-Dimethoxy-4-(3-aminophenoxy)quinoline (54 mg) and commercially available 4-t-butyl benzoic acid (102 mg) were dissolved in N,N-dimethylformamide (3 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (106 mg) was added, and the admixture was stirred at room temperature for 6 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 29 mg of the title compound (yield: 35%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 34 (s, 9H), 4. 01 (s, 3H), 4. 04 (s, 3H), 6. 55 (d, J=4. 9Hz, 1H), 6. 97 (d, J=7. 3Hz, 1H), 7. 29~7. 68 (m, 7H), 7. 85 (d, J=7. 9Hz, 2H), 8. 48 (d, J=4. 9Hz, 1H), 8. 59 (brs, 1H)

Mass spectrometry data (FD-MS, m/z) : 456 (M⁺)

Example 90

35 N-[3-[6,7-Dimethoxy-4-quinolyl]thio]phenyl]-[4-t-butylphenyl]carboxamide [160]

40 6,7-Dimethoxy-4-(3-aminophenylthio)quinoline (62 mg) and commercially available 4-t-butyl benzoic acid (109 mg) were dissolved in N,N-dimethylformamide (3 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (112 mg) was added, and the admixture was stirred at room temperature for 25 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 54 mg of the title compound (yield: 57%).

45 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 31 (s, 9H), 4. 00 (s, 3H), 4. 01 (s, 3H), 6. 83 (d, J=4. 9Hz, 1H), 7. 20~7. 99 (m, 9H), 8. 06 (m, 1H), 8. 39 (d, J=4. 9Hz, 1H), 8. 60 (brs, 1H)

Mass spectrometry data (FD-MS, m/z) : 472 (M⁺)

45 Example 91

N-[4-[6,7-Dimethoxy-4-quinolyl]thio]phenyl]-[4-butylphenyl]carboxamide [161]

50 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (62 mg) and commercially available 4-butyl benzoic acid (104 mg) were dissolved in N,N-dimethylformamide (3 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (117 mg) was added, and the admixture was stirred at room temperature for 21 hours. The reaction mixture was then purified in the same manner as described in Example 51 to obtain 21 mg of the title compound (yield: 22%).

55 ¹H-NMR (CDCl₃, 500MHz) : δ 0. 94 (t, J=7. 3Hz, 3H), 1. 38 (m, 2H), 1. 63 (m, 2H), 2. 69 (t, J=7. 9Hz, 2H), 4. 03 (s, 3H), 4. 05 (s, 3H), 6. 72 (d, J=4. 9Hz, 1H), 7. 30 (d, J=7. 9Hz, 2H), 7. 39 (s, 1H), 7. 42 (s, 1H), 7. 57 (d, J=8. 5Hz, 2H), 7. 78 (d, J=8. 5Hz, 2H), 7. 81 (d, J=7. 9Hz, 2H), 8. 08 (s, 1H), 8. 42 (d, J=5. 5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 472 (M⁺)

Example 92

5 N- { 4 - [6 , 7 - Dimethoxy - 4 - quinolyl) oxy] phenyl } - N' - (4 -
methoxythiophenyl) urea [163]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) was dissolved in toluene (3 ml) with heat, 4-methylthiophenyl
 isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 8 minutes. The separated crystals were
 filtered and washed with toluene to obtain 62 mg of the title compound (yield: 76%).

15 ¹H-NMR (DMSO-d₆, 500MHz) : δ 2. 44 (s, 3H), 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 44 (d, J=4. 9Hz, 1H), 7. 19 (d, J=9.
 2Hz, 2H), 7. 23 (d, J=8. 5Hz, 2H), 7. 38 (s, 1H), 7. 44 (d, J=9. 2Hz, 2H), 7. 52 (s, 1H), 7. 58 (d, J=8. 6Hz, 2H), 8. 46
 (d, J=4. 9Hz, 1H), 8. 70 (s, 1H), 8. 79 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 461 (M⁺)

Example 93

20 N- (3 - Ethoxycarbonylphenyl) - N' - { 4 - [(6 , 7 - dimethoxy - 4 -
quinolyl) oxy] phenyl) urea [164]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) was dissolved in toluene (5 ml) with heat, 3-ethoxycarbonyl-
 phenyl isocyanate (284 mg) was added, and the admixture was refluxed with heat for 1 hour. The resulting residue was
 purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 18 mg of the title com-
 pound (yield: 20%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 38 (m, 3H), 3. 98 (s, 3H), 4. 05 (s, 3H), 4. 35 (m, 2H), 6. 45 (d, J=5. 5Hz, 1H), 7.
 12 (d, J=9. 2Hz, 2H), 7. 40 (s, 1H), 7. 47 (d, J=9. 2Hz, 2H), 7. 47 (d, J=8. 6Hz, 2H), 7. 58 (s, 1H), 7. 96 (d, J=9. 2Hz,
 2H), 8. 05 (s, 1H), 8. 17 (s, 1H), 8. 47 (d, J=5. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 487 (M⁺)

Example 94

35 N - (4 - Chlorophenyl) - N' - { 4 - [(6 , 7 - dimethoxy - 4 -
quinolyl) oxy] phenyl) urea [165]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 4-chlorophenyl iso-
 cyanate (0.2 ml) was added, and the admixture was refluxed with heat for 1 hour. The separated crystals were filtered
 and washed with toluene to obtain 43 mg of the title compound (yield: 55%).

50 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 44 (d, J=5. 5Hz, 1H), 7. 20 (d, J=9. 2Hz, 2H), 7. 32
 (d, J=8. 5Hz, 2H), 7. 38 (s, 1H), 7. 49 (d, J=9. 2Hz, 2H), 7. 51 (s, 1H), 7. 58 (d, J=9. 2Hz, 2H), 8. 46 (d, J=4. 9Hz,
 1H), 8. 83 (brs, 1H), 8. 83 (brs, 1H)
 Mass spectrometry data (FD-MS, m/z) : 449 (M⁺), 451 (M⁺+2)

Example 95

5 N - (2 - Isopropylphenyl) - N ' - { 4 - [(6 , 7 - dimethoxy - 4 -
quinolyl) oxy] phenyl } urea [166]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (44 mg) was dissolved in toluene (5 ml) with heat, 2-isopropylphenyl
 15 isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 80 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 14 mg of the title compound (yield: 20%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 1.21 (m, 6H), 3.21 (m, 1H), 4.04 (s, 3H), 4.04 (s, 3H), 6.42 (m, 1H), 6.63 (m, 1H),
 15 7.09-7.55 (m, 11H), 8.46 (m, 1H)
 Mass spectrometry data (FD-MS, m/z) : 457 (M⁺)

Example 96

20 N - { 4 - [(6 , 7 - dimethoxy - 4 - quinolyl) oxy] phenyl } - N ' - phenylurea
[167]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, phenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 50 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 21 mg of the title compound (yield: 41%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 4.04 (s, 3H), 4.04 (s, 3H), 6.61 (m, 1H), 7.05 (m, 1H), 7.36-7.44 (m, 10H), 7.99
 30 (s, 1H), 8.31 (s, 1H), 8.36 (m, 1H)
 Mass spectrometry data (FD-MS, m/z) : 431 (M⁺)

Example 97

35 N - { 4 - [(6 , 7 - dimethoxy - 4 - quinolyl) oxy] phenyl } - N ' - (2 -
nitrophenyl) urea [168]

40 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (83 mg) was dissolved in toluene (8 ml) with heat, 4-nitrophenyl isocyanate (370 mg) was added, and the admixture was refluxed with heat for 40 minutes. The deposited crystals were filtered and washed with toluene to obtain 58 mg of the title compound (yield: 45%).

45 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3.94 (s, 3H), 3.95 (s, 3H), 6.46 (d, J=5.5Hz, 1H), 7.22 (m, 1H), 7.23 (d, J=9.2Hz, 2H), 7.38 (s, 1H), 7.51 (s, 1H), 7.62 (d, J=9.2Hz, 2H), 7.71 (m, 1H), 8.11 (m, 1H), 8.31 (m, 1H), 8.46 (d, J=5.5Hz, 1H), 9.62 (s, 1H), 9.96 (s, 1H)
 50 Mass spectrometry data (FD-MS, m/z) : 460 (M⁺)

Example 98

5 N-(2-Aminophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [169]

10 N-[4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl]-N'-(2-nitrophenyl)urea (42 mg) was dissolved in N,N-dimethylformamide/ethyl acetate (12 ml/6 ml), 20% palladium hydroxide-carbon (70 mg) was added, and the admixture was stirred at room temperature under hydrogen for 3 hours. The reaction mixture was filtered using Celite, after which the filtrate was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation to obtain 39 mg of the title compound (yield: 100%).

15 $^1\text{H-NMR}$ (DMSO- d_6 , 500MHz) : δ 3.94 (s, 3H), 3.95 (s, 3H), 4.77 (brs, 2H), 6.44 (d, $J=5.5\text{Hz}$, 1H), 6.58 (m, 1H), 6.75 (m, 1H), 6.85 (m, 1H), 7.18 (d, $J=8.5\text{Hz}$, 2H), 7.34 (m, 1H), 7.38 (s, 1H), 7.52 (s, 1H), 7.58 (d, $J=9.2\text{Hz}$, 2H), 8.29 (s, 1H), 8.46 (d, $J=4.9\text{Hz}$, 1H), 8.92 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 430 (M^+)

20 Example 99

25 N-(4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl)-N'-(3-nitrophenyl)urea [170]

30 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (83 mg) was dissolved in toluene (6 ml) with heat, 3-nitrophenyl isocyanate (384 mg) was added, and the admixture was refluxed with heat for 40 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 44 mg of the title compound (yield: 34%).

35 $^1\text{H-NMR}$ (DMSO- d_6 , 500MHz) : δ 3.99 (s, 3H), 4.04 (s, 3H), 6.43 (d, $J=4.9\text{Hz}$, 1H), 7.10 (d, $J=9.2\text{Hz}$, 2H), 7.38 (m, 2H), 7.47 (d, $J=8.6\text{Hz}$, 2H), 7.57 (s, 1H), 7.81 (m, 2H), 8.19 (s, 1H), 8.31 (s, 1H), 8.46 (d, $J=4.9\text{Hz}$, 1H), 8.59 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 460 (M^+)

Example 100

40 N-[4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl]-N'-octylurea [171]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, octyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 2 hours. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 32 mg of the title compound (yield: 41%).

50 $^1\text{H-NMR}$ (CDCl₃, 500MHz) : δ 0.87 (m, 3H), 1.26-1.30 (m, 10H), 1.53 (m, 2H), 3.27 (m, 2H), 4.03 (s, 3H), 4.03 (s, 3H), 5.04 (m, 1H), 6.44 (d, $J=5.5\text{Hz}$, 1H), 6.97 (s, 1H), 7.10 (d, $J=8.6\text{Hz}$, 2H), 7.41 (s, 1H), 7.42 (d, $J=8.6\text{Hz}$, 2H), 7.55 (s, 1H), 8.46 (d, $J=4.9\text{Hz}$, 1H)
 Mass spectrometry data (FD-MS, m/z) : 451 (M^+)

Example 101

5 N-(3-Aminophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [172]

10 N-[4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl]-N'-(3-nitrophenyl)urea (28 mg) was dissolved in N,N-dimethylformamide/ethyl acetate (5 ml/2.5 ml), 20% palladium hydroxide-carbon (97 mg) was added, and the admixture was stirred at room temperature under hydrogen for 3 hours. The reaction mixture was filtered using Celite, the filtrate was washed with brine and then dried with anhydrous sodium sulfate. The solvent was then removed by reduced-pressure distillation to obtain 13 mg of the title compound (yield: 51%).

15 $^1\text{H-NMR}$ (CDCl₃, 500MHz) : δ 4.02 (s, 3H), 4.03 (s, 3H), 6.41 (m, 1H), 6.41 (d, J=5.5Hz, 1H), 6.61 (m, 1H), 6.90 (s, 1H), 7.05 (m, 1H), 7.09 (d, J=8.5Hz, 2H), 7.40 (s, 1H), 7.43 (m, 1H), 7.47 (d, J=8.5Hz, 2H), 7.55 (s, 1H), 8.03 (s, 1H), 8.44 (d, J=5.5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 430 (M⁺)

20 Example 102

25 N-allyl-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [173]

30 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in N,N-dimethylformamide (5 ml), allyl isocyanate (0.2 ml) was added, and the admixture was stirred at 80 °C for 15 hours with heat. Water was added to the reaction mixture, the admixture was extracted 2 times with ethyl acetate, and the organic layer was washed with brine and then dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 61 mg of the title compound (yield: 96%).

35 $^1\text{H-NMR}$ (CDCl₃, 500MHz) : δ 3.90 (m, 2H), 4.03 (s, 3H), 4.03 (s, 3H), 5.12 (d, J=10.4Hz, 1H), 5.23 (d, J=17.7Hz, 1H), 5.62 (s, 1H), 5.88 (m, 1H), 6.41 (d, J=4.9Hz, 1H), 7.08 (d, J=8.5, 2H), 7.39 (s, 1H), 7.44 (d, J=8.5Hz, 2H), 7.54 (s, 1H), 7.75 (s, 1H), 8.44 (d, J=5.5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 379 (M⁺)

40 Example 103

45 N-[4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl]-N'-(1-naphthyl)urea [174]

50 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, 1-naphthyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 20 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 41 mg of the title compound (yield: 52%).

55 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3.95 (s, 3H), 3.95 (s, 3H), 6.45 (d, J=5.5Hz, 1H), 7.21 (d, J=9.2Hz, 2H), 7.38 (s, 1H), 7.48-7.65 (m, 7H), 7.92-8.15 (m, 3H), 8.46 (d, J=4.9Hz, 1H), 8.80 (s, 1H), 9.20 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 465 (M⁺)

Example 104

5 N - (2 - B i p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
quinolyl)oxy]phenyl}urea [175]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 2-biphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 30 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 56 mg of the title compound (yield: 64%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 3. 97 (s, 3H), 4. 04 (s, 3H), 6. 35 (d, J=5. 5Hz, 1H), 6. 96 (s, 1H), 7. 40 (d, J=9. 2Hz, 2H), 7. 14~7. 39 (m, 11H), 7. 54 (s, 1H), 7. 89 (brs, 1H), 8. 08 (d, J=8. 6Hz, 1H), 8. 33 (d, J=5. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 491 (M⁺)

Example 105

20 N - (4 - E t h y l p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
quinolyl)oxy]phenyl}urea [188]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, 4-ethylphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 90 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 42 mg of the title compound (yield: 56%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 18 (m, 3H), 2. 58 (m, 2H), 3. 99 (s, 3H), 4. 02 (s, 3H), 6. 39 (d, J=5. 5Hz, 1H), 7. 07 (d, J=9. 2Hz, 2H), 7. 11 (d, J=7. 9Hz, 2H), 7. 25 (d, J=8. 5Hz, 2H), 7. 40 (s, 1H), 7. 42 (d, J=8. 5Hz, 2H), 7. 55 (s, 1H), 7. 60 (s, 1H), 7. 81 (s, 1H), 8. 43 (d, J=4. 9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 443 (M⁺)

Example 106

35 N - B e n z o y l - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 - q u i n o l y l) o x y] p h e n y l } u r e a
 40 [189]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, benzoyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 50 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 11 mg of the title compound (yield: 15%).

50 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 06 (s, 3H), 4. 07 (s, 3H), 6. 49 (d, J=4. 9Hz, 1H), 7. 20 (d, J=9. 2Hz, 2H), 7. 43 (s, 1H), 7. 54 (m, 2H), 7. 58 (s, 1H), 7. 65 (m, 1H), 7. 71 (d, J=9. 2Hz, 2H), 8. 04 (d, J=7. 9Hz, 2H), 8. 50 (d, J=5. 5Hz, 1H), 9. 53 (s, 1H), 11. 04 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 443 (M⁺)

Example 107

5 N-Ethoxycarbonyl-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [190]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, ethoxycarbonyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 15 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 20 mg of the title compound (yield: 28%).

15 $^1\text{H-NMR}$ (CDCl_3 , 500MHz) : δ 1.37 (t, $J=7.3\text{Hz}$, 3H), 4.10 (s, 3H), 4.17 (s, 3H), 4.31 (q, $J=7.3\text{Hz}$, 2H), 6.70 (d, $J=6.1\text{Hz}$, 1H), 7.20 (d, $J=8.6\text{Hz}$, 2H), 7.64 (s, 1H), 7.72 (d, $J=9.2\text{Hz}$, 2H), 8.12 (s, 1H), 8.50 (d, $J=6.7\text{Hz}$, 1H), 10.08 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 411 (M^+)

Example 108

20 N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methylphenyl)urea [56]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, 2-methylphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 15 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 61 mg of the title compound (yield: 82%).

30 $^1\text{H-NMR}$ (CDCl_3 , 500MHz) : δ 2.20 (s, 3H), 4.00 (s, 3H), 4.03 (s, 3H), 4.31 (q, $J=7.3\text{Hz}$, 2H), 6.40 (d, $J=5.5\text{Hz}$, 1H), 7.05~7.20 (m, 6H), 7.39 (s, 1H), 7.42 (d, $J=8.5\text{Hz}$, 2H), 7.55 (s, 1H), 7.60 (d, $J=7.9\text{Hz}$, 2H), 7.80 (s, 1H), 8.45 (d, $J=5.5\text{Hz}$, 1H)

35 Mass spectrometry data (FD-MS, m/z) : 429 (M^+)

Example 109

40 N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(3-methylphenyl)urea [55]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, 3-methylphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 15 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 41 mg of the title compound (yield: 56%).

50 $^1\text{H-NMR}$ (CDCl_3 , 500MHz) : δ 2.32 (s, 3H), 4.02 (s, 3H), 4.04 (s, 3H), 6.43 (d, $J=5.5\text{Hz}$, 1H), 6.93 (d, $J=7.3\text{Hz}$, 1H), 7.10~7.22 (m, 6H), 7.41 (s, 1H), 7.44~7.47 (m, 3H), 7.56 (s, 1H), 8.46 (d, $J=5.5\text{Hz}$, 1H)

Mass spectrometry data (FD-MS, m/z) : 429 (M^+)

Example 110

5 N-(2-Fluorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [60]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, 2-fluorophenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 15 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 54 mg of the title compound (yield: 73%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 4.01 (s, 3H), 4.04 (s, 3H), 6.44 (d, J=5.5Hz, 1H), 6.97~7.04 (m, 2H), 7.10~7.12 (m, 3H), 7.42 (s, 1H), 7.49 (d, J=9.2Hz, 2H), 7.57 (s, 1H), 7.73 (s, 1H), 8.17 (m, 1H), 8.35 (s, 1H), 8.48 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 433 (M⁺)

Example 111

20

N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}-N'-propylurea
[194]

25

30 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) was dissolved in N,N-dimethylformamide (3 ml), propyl isocyanate (0.2 ml) was added, and the admixture was stirred at 80 °C for 24 hours. Water was added to the reaction mixture, the admixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 59 mg of the title compound (yield: 84%).

35 ¹H-NMR (CDCl₃, 500MHz) : δ 0.93 (m, 3H), 1.55 (m, 2H), 3.24 (m, 2H), 4.02 (s, 3H), 4.02 (s, 3H), 5.47 (t, J=5.5Hz, 1H), 6.41 (d, J=4.9Hz, 1H), 7.08 (d, J=8.5Hz, 2H), 7.39 (s, 1H), 7.43 (d, J=9.2Hz, 2H), 7.55 (s, 1H), 7.60 (brs, 1H), 8.44 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 381 (M⁺)

Example 112

40

N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}-N'-(4-phenylcarbonylphenyl)urea [195]

45

50 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) was suspended in toluene (5 ml), triphosgene (53 mg) was added, and the admixture was refluxed with heat for 20 minutes. 4-Aminobenzophenone (85 mg) was added to the reaction mixture, and the admixture was refluxed for 1 hour with heat. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 19 mg of the title compound (yield: 21%).

55 ¹H-NMR (CDCl₃, 500MHz) : δ 4.01 (s, 3H), 4.04 (s, 3H), 6.44 (d, J=4.9Hz, 1H), 7.12 (d, J=9.2Hz, 2H), 7.41 (s, 1H), 7.46~7.80 (m, 12H), 8.14 (s, 1H), 8.30 (s, 1H), 8.47 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 519 (M⁺)

Example 113

N-Hexyl-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea
[196]

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in N,N-dimethylformamide (3 ml), hexyl isocyanate (0.2 ml) was added, and the admixture was stirred at 60 °C for 15 hours. After the addition of water, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 63 mg of the title compound (yield: 84%).

15 $^1\text{H-NMR}$ (CDCl_3 , 500MHz) : δ 0.85 (m, 3H), 1.25~1.47 (m, 6H), 1.50 (m, 2H), 3.26 (q, $d=6.7\text{Hz}$, 2H), 4.02 (s, 3H), 4.02 (s, 3H), 5.68 (brs, 1H), 6.40 (d, $J=5.5\text{Hz}$, 1H), 7.07 (d, $J=9.2\text{Hz}$, 2H), 7.39 (s, 1H), 7.44 (d, $J=9.2\text{Hz}$, 2H), 7.55 (s, 1H), 7.94 (s, 1H), 8.43 (d, $J=4.9\text{Hz}$, 1H)
Mass spectrometry data (FD-MS, m/z) : 423 (M^+)

Example 114

25 N - (5 - Indanyl) - N ' - { 4 - [(6 , 7 - dimethoxy - 4 -
quinolyl)oxy]phenyl}urea [197]

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was suspended in toluene (5 ml), triphosgene (54 mg) was added, and the admixture was refluxed with heat for 12 minutes. 4-Aminoisindan (36 mg) was added, and the admixture was refluxed with heat for 36 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 13 mg of the title compound (yield: 16%).

¹H-NMR (CDCl₃, 500MHz) : δ 2.04 (m, 2H), 2.82~2.86 (m, 4H), 4.01 (s, 3H), 4.03 (s, 3H), 6.40 (d, J=5.5Hz, 1H), 7.03 (m, 1H), 7.08 (d, J=8.5Hz, 2H), 7.13 (m, 1H), 7.32 (s, 1H), 7.40~7.57 (m, 6H), 8.44 (d, J=4.9Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 455 (M⁺)

Example 115

45 N-(3,4-Dimethoxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [1981]

3,4-Dimethoxyaniline (42 mg) was dissolved in toluene (5 ml), triphosgene (24 mg) was added, and the admixture was refluxed with heat for 22 minutes. 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) (52 mg) was added, and the admixture was refluxed with heat for 18 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 15 mg of the title compound (yield: 18%).

¹H-NMR (CDCl₃, 500MHz) : δ 3.84 (s, 3H), 3.85 (s, 3H), 4.01 (s, 3H), 4.04 (s, 3H), 6.43 (d, J=4.9Hz, 1H), 6.75–6.80 (m, 2H), 7.10 (d, J=9.2Hz, 2H), 7.16 (s, 1H), 7.38 (s, 1H), 7.41 (s, 1H), 7.45 (d, J=8.5Hz, 2H), 7.56

(s, 1H), 7.59 (s, 1H), 8.46 (d, J=4.9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 475 (M⁺)

Example 116

5

N-(3,4-Ethylenedioxypyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [199]

10

3,4-Ethylenedioxylaniline (80 mg) was dissolved in toluene (5 ml), triethylamine (0.5 ml) and then triphosgene (50 mg) were added, and the admixture was refluxed with heat for 1 hour. 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was added, and the admixture was refluxed with heat for 100 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 62 mg of the title compound (yield: 74%).

20

¹H-NMR (DMSO-d₆, 500MHz) : δ 3.94 (s, 3H), 3.94 (s, 3H), 4.19~4.21 (m, 4H), 6.43 (d, J=4.9Hz, 1H), 6.74~6.78 (m, 2H), 7.09 (s, 1H), 7.17 (d, J=9.2Hz, 2H), 7.37 (s, 1H), 7.51 (s, 1H), 7.56 (d, J=8.5Hz, 2H), 8.45 (d, J=4.9Hz, 1H), 8.47 (s, 1H), 8.69 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 473 (M⁺)

25

Example 117

N-Methyl-N-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)-N'-(4-methoxyphenyl)urea [200]

30

Formic acid (0.13 ml) was added to acetic anhydride (0.27 ml), and the admixture was stirred at 60 °C for 2 hours. A solution of 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (303 mg) in tetrahydrofuran (8 ml) was added to the reaction mixture, and the admixture was stirred at room temperature for 45 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 327 mg of 6,7-dimethoxy-4-(4-formylaminophenoxy)quinoline.

40

6,7-Dimethoxy-4-(4-formylaminophenoxy)quinoline (317 mg) thus obtained was dissolved in tetrahydrofuran (9 ml), lithium aluminum hydride (181 mg) was added, and the admixture was stirred at room temperature for 2 hours. After the addition of aqueous ammonium chloride, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 239 mg of 6,7-dimethoxy-4-(4-methylaminophenoxy)quinoline.

45

6,7-Dimethoxy-4-(4-methylaminophenoxy)quinoline (49 mg) thus obtained was dissolved in toluene (5 ml) with heat, 4-methoxyphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 12 hours. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 47 mg of the title compound (yield: 51%).

50

¹H-NMR (CDCl₃, 500MHz) : δ 3.38 (s, 3H), 3.77 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.14 (brs, 1H), 6.59 (d, J=5.5Hz, 1H), 6.82 (d, J=9.2Hz, 2H), 7.21 (d, J=9.2Hz, 2H), 7.29 (d, J=9.2Hz, 2H), 7.44 (d, J=8.6Hz, 2H), 7.45 (s, 1H), 7.52 (s, 1H), 8.55 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 459 (M⁺)

55

Example 118

5 N-Methyl-N-phenyl-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [201]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (72 mg) was suspended in toluene (7 ml), triphosgene (52 mg) was added, and the admixture was refluxed with heat for 3 hours. N-Methylaniline (0.05 ml) was added to the reaction mixture, and the admixture was refluxed for 1 hour with heat. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 48 mg of the title compound (yield: 46%).

15

1H-NMR (CDCl₃, 500MHz) : δ 3.37 (s, 3H), 4.04 (s, 3H), 4.04 (s, 3H), 6.32 (brs, 1H), 6.41 (d, J=4.9Hz, 1H), 7.07 (d, J=9.2Hz, 2H), 7.37~7.53 (m, 8H), 7.54 (s, 1H), 8.45 (d, J=5.5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 429 (M⁺)

20 Example 119

25 N-Methyl-N-(4-methoxyphenyl)-N'-methyl-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [202]

30 N-(4-Methoxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea (99 mg) was dissolved in N,N-dimethylformamide (3 ml), sodium hydride (42 mg) was added, and the admixture was stirred at room temperature for 20 minutes, methyl iodide (0.03 ml) was added, and the admixture was stirred at the same temperature for 1 hour. After the addition of aqueous ammonium chloride, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 91 mg of the title compound (yield: 87%).

35

1H-NMR (CDCl₃, 500MHz) : δ 3.23 (s, 3H), 3.24 (s, 3H), 3.75 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.27 (d, J=5.5Hz, 1H), 6.69 (d, J=8.5Hz, 2H), 6.81 (d, J=9.2Hz, 2H), 6.89 (d, J=9.2Hz, 2H), 6.91 (d, J=9.2Hz, 2H), 7.42 (s, 1H), 7.51 (s, 1H), 8.53 (d, J=4.9Hz, 1H)
 40 Mass spectrometry data (FD-MS, m/z) : 473 (M⁺)

Example 120 (Reference Example)

3,4-Dichlorophenyl 4-methoxyphenyl ketone

45 To commercially available nitromethane (10 ml) were added commercially available anisole (1.081 g), commercially available 3,4-dichlorobenzoyl chloride (2.095 g) and commercially available ytterbium(III) trifluoromethanesulfonate (620 mg), and the admixture was stirred at 60 °C for 8 hours. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 270 mg of the title compound (yield: 10%).

50

1H-NMR (CDCl₃, 500MHz) : δ 3.90 (s, 3H), 6.98 (d, J=9.2Hz, 2H), 7.56 (s, 1H), 7.58 (d, J=1.8Hz, 1H), 7.79 (d, J=9.2Hz, 2H), 7.84 (d, J=1.8Hz, 1H)
 55 Mass spectrometry data (FD-MS, m/z) : 280 (M⁺), 282 (M⁺⁺)

Example 121 (Reference Example)

3,4-Dichlorophenyl 4-hydroxyphenyl ketone

5 3,4-Dichlorophenyl 4-methoxyphenyl ketone (235 mg) obtained in Example 120 was dissolved in dichloromethane (2 ml), a solution of 1.0 M boron tribromide in dichloromethane (7 ml) was added while cooled in ice, and the admixture was stirred at room temperature for two days. The reaction mixture was then poured into ice water and partitioned between water and chloroform. The chloroform layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 173 mg of the title compound (yield: 77%).

10 ¹H-NMR (DMSO-d₆, 500MHz) : δ 6. 91 (d, J=8. 5Hz, 2H), 7. 62 (dd, J=1. 8, 8. 6Hz, 1H), 7. 68 (d, J=8. 5Hz, 2H), 7. 80 (d, J=7. 9Hz, 1H), 7. 85 (d, J=1. 8Hz, 1H), 10. 55 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 266 (M⁺), 268 (M⁺+2)

15 Example 122

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(3,4-dichlorophenyl)methanone [177]

20 Under argon, 3,4-dichlorophenyl 4-hydroxyphenyl ketone (154 mg) obtained in Example 121 and 4-dimethylaminopyridine (77 mg) were added to xylene (5 ml), and the admixture was stirred at room temperature for 3 hours. 4-Chloro-6,7-dimethoxyquinoline (129 mg) was added, and the admixture was refluxed with heat for 21 hours. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by thin layer chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 81 mg of the title compound (yield: 31%).

25 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 03 (s, 3H), 4. 07 (s, 3H), 6. 68 (d, J=5. 5Hz, 1H), 7. 28 (d, J=8. 5Hz, 2H), 7. 46 (s, 1H), 7. 47 (s, 1H), 7. 60 (d, J=8. 5Hz, 1H), 7. 66 (dd, J=1. 8, 8. 6Hz, 1H), 7. 90 (d, J=9. 2Hz, 2H), 7. 91 (d, J=1. 8Hz, 1H), 8. 60 (d, J=4. 9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 453 (M⁺), 455 (M⁺+2)

Example 123 (Reference Example)

4-(4-Hydroxybenzoyl)benzonitrile

35 4-Tri-n-butylin-1-methoxymethylphenol (1.282 g) obtained in Example 22 and commercially available 4-cyanobenzoyl chloride (497 mg) were dissolved in chloroform (5 ml), commercially available bis(triphenylphosphine)palladium(II) chloride (8 mg) was added, and the admixture was refluxed with heat for 11 hours. The reaction mixture was partitioned in the same manner as described in Example 23, and the resulting ether layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue (859 mg) was dissolved in tetrahydrofuran (2 ml), water (5 ml) and 6 N aqueous hydrochloric acid (12 ml) were added, and the admixture was refluxed with heat for 4 hours. The reaction mixture was partitioned between brine and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate to obtain 250 mg of the title compound (yield: 37%).

40 ¹H-NMR (DMSO-d₆, 500MHz) : δ 6. 91 (d, J=9. 2Hz, 2H), 7. 67 (d, J=8. 5Hz, 2H), 7. 80 (d, J=7. 9Hz, 2H), 8. 01 (d, J=8. 6Hz, 2H), 10. 57 (s, 1H)
 45 Mass spectrometry data (FD-MS, m/z) : 223 (M⁺)

Example 124

4-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]benzoyl}benzonitrile [178]

50 Under argon, 4-(4-hydroxybenzoyl)benzonitrile (230 mg) obtained in Example 123 and 4-dimethylaminopyridine (138 mg) were added to xylene (5 ml), and the admixture was stirred at room temperature for 1 hour. 4-Chloro-6,7-dimethoxyquinoline (230 mg) was added, and the admixture was refluxed with heat for 20 hours. The reaction mixture

was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate and then by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1) to obtain 199 mg of the title compound (yield: 47%).

5

¹H-NMR (CDCl₃, 500MHz) : δ 4.03 (s, 3H), 4.06 (s, 3H), 6.68 (d, J=5.5Hz, 1H), 7.29 (d, J=8.5Hz, 2H), 7.45 (s, 1H), 7.46 (s, 1H), 7.82 (d, J=7.9Hz, 2H), 7.90 (d, J=8.6Hz, 2H), 7.91 (d, J=8.5Hz, 2H), 8.60 (d, J=5.5Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 410 (M⁺)

10 Example 125 (Reference Example)

4-Methoxyphenyl 2-methylphenyl ketone

To commercially available nitromethane (10 ml) were added commercially available anisole (1.081 g), commercially available 2-methylbenzoyl chloride (1.546 g) and commercially available ytterbium(III) trifluoromethanesulfonate (620 mg), and the admixture was stirred at 60 °C for 7 hours. The reaction mixture was treated in the same manner as described in Example 120 to obtain 1.679 g of the title compound (yield: 74%).

20

Mass spectrometry data (FD-MS, m/z) : 226 (M⁺)

20 Example 126 (Reference Example)

4-Hydroxyphenyl 2-methylphenyl ketone

25 4-Methoxyphenyl 2-methylphenyl ketone (1.660 g) obtained in Example 125 was dissolved in chloroform (10 ml), a solution of 1.0 M boron tribromide in dichloromethane (29 ml) was added while cooled in ice, and the admixture was stirred at room temperature overnight. A solution of 1.0 M boron tribromide in dichloromethane (15 ml) was further added, and the admixture was stirred at room temperature for 2 days. The reaction mixture was then treated in the same manner as described in Example 121 to obtain 1.501 g of the title compound (yield: 96%).

30

¹H-NMR (CDCl₃, 500MHz) : δ 2.30 (s, 3H), 6.87 (d, J=8.5Hz, 2H), 7.22~7.29 (m, 3H), 7.37 (td, J=1.2, 7.3Hz, 1H), 7.73 (d, J=8.5Hz, 2H)
Mass spectrometry data (FD-MS, m/z) : 212 (M⁺)

35 Example 127

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(2-methylphenyl)methanone [180]

Under argon, 4-hydroxyphenyl 2-methylphenyl ketone (1.334 g) obtained in Example 126 and 4-dimethylaminopyridine (845 mg) were added to xylene (15 ml), and the admixture was stirred at room temperature for 1 hour. 4-Chloro-6,7-dimethoxyquinoline (1.406 g) was added, and the admixture was refluxed with heat for 23 hours. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate and then with chloroform, followed by thin layer chromatography on silica gel eluting with hexane/acetone (2/1), to obtain 1.258 g of the title compound (yield: 50%).

50

¹H-NMR (CDCl₃, 500MHz) : δ 2.37 (s, 3H), 4.02 (s, 3H), 4.06 (s, 3H), 6.65 (d, J=4.9Hz, 1H), 7.23 (d, J=8.6Hz, 2H), 7.25~7.35 (m, 3H), 7.39~7.42 (m, 1H), 7.45 (s, 1H), 7.46 (s, 1H), 7.91 (d, J=8.5Hz, 2H), 8.57 (d, J=5.5Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 399 (M⁺)

Example 128

{3-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}phenylmethanone [181]

A mixture of 4-chloro-6,7-dimethoxyquinoline (112 mg) and commercially available 3-hydroxybenzophenone (297 mg) was stirred at 170 °C for 10 minutes, the reaction mixture was then purified by thin layer chromatography on silica

gel eluting with hexane/acetone (2/1) to obtain 126 mg of the title compound (yield: 65%).

¹H-NMR (CDCl₃, 90MHz) : δ 4.04 (s, 3H), 4.05 (s, 3H), 6.53 (d, J=5.3Hz, 1H), 7.34-7.88 (m, 11H), 8.53 (d, J=5.3Hz, 1H)

5 Mass spectrometry data (FD-MS, m/z) : 385 (M⁺)

Example 129 (Reference Example)

2-Furoyl 4-hydroxyphenyl ketone

10 4-Tri-n-butylin-1-methoxymethylphenol (1.282 g) obtained in Example 22 and commercially available 2-furoyl chloride (392 mg) were dissolved in chloroform (5 ml), commercially available bis(triphenylphosphine)palladium(II) chloride (8 mg) was added, and the admixture was refluxed for 11 hours. The reaction mixture was partitioned in the same manner as described in Example 23, and the resulting ether layer was dried with anhydrous magnesium sulfate. After 15 removing the solvent by reduced-pressure distillation, the resulting residue (662 mg) was dissolved in tetrahydrofuran (2 ml), water (5 ml) and 6 N aqueous hydrochloric acid (12 ml) were added, and the admixture was refluxed for 3 hours with heat. The reaction mixture was treated in the same manner as described in Example 123 to obtain 218 mg of the title compound (yield: 39%).

20 ¹H-NMR (DMSO-d₆, 500MHz) : δ 6.76 (dd, J=1.2, 3.1Hz, 1H), 6.91 (d, J=8.5Hz, 2H), 7.33 (d, J=3.1Hz, 1H), 7.87 (d, J=8.5Hz, 2H), 8.06 (d, J=1.2Hz, 1H), 10.39 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 188 (M⁺)

Example 130

2-Furoyl-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]methanone [182]

Under argon, 2-furoyl 4-hydroxyphenyl ketone (205 mg) obtained in Example 129 and 4-dimethylaminopyridine (146 mg) were added to xylene (5 ml), and the admixture was stirred at room temperature for 1 hour. 4-Chloro-6,7-dimethoxyquinoline (244 mg) was added, and the admixture was then refluxed with heat for 20 hours. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate and then with chloroform, followed by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1), to obtain 192 mg of the title compound (yield: 47%).

¹H-NMR (CDCl₃, 500MHz) : δ 4.03 (s, 3H), 4.07 (s, 3H), 6.63 (dd, J=1.8, 3.7Hz, 1H), 6.65 (d, J=5.5Hz, 1H), 7.28 (d, J=8.5Hz, 2H), 7.32 (d, J=3.7Hz, 1H), 7.47 (s, 1H), 7.48 (s, 1H), 7.73 (d, J=1.8Hz, 1H), 8.14 (d, J=9.2Hz, 2H), 8.58 (d, J=5.5Hz, 1H)

40 Mass spectrometry data (FD-MS, m/z) : 375 (M⁺)

Example 131 (Reference Example)

4-Methoxyphenyl 3-methylphenyl ketone

45 To commercially available nitromethane (5 ml) were added commercially available anisole (541 mg), commercially available 3-methylbenzoyl chloride (773 mg) and commercially available scandium(III) trifluoromethanesulfonate (49 mg), and the admixture was stirred at 60 °C overnight. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/acetone to obtain 635 mg of the title compound (yield: 56%).

Mass spectrometry data (FD-MS, m/z) : 226 (M⁺)

Example 132 (Reference Example)

4-Hydroxyphenyl 3-methylphenyl ketone

5 4-Methoxyphenyl 3-methylphenyl ketone (603 mg) obtained in Example 131 was dissolved in dichloromethane (3 ml), a 1.0 M boron tribromide-dichloromethane solution (11 ml) was added while cooled in ice, and the admixture was stirred at room temperature for 22 hours, after which the reaction mixture was treated in the same manner as described in Example 121 to obtain 316 mg of the title compound (yield: 56%).

10 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 2. 38 (s, 3H), 6. 89 (d, J=8. 6Hz, 2H), 7. 37~7. 47 (m, 4H), 7. 65 (d, J=8. 6Hz, 2H), 10. 42 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 212 (M⁺)

Example 133

15 {4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(3-methylphenyl)methanone [183]

20 Under argon, 4-hydroxyphenyl 3-methylphenyl ketone (307 mg) obtained in Example 132 and 4-dimethylaminopyridine (194 mg) were added to xylene (5 ml), and the admixture was stirred at room temperature for 1 hour. 4-Chloro-6,7-dimethoxyquinoline (324 mg) was added, and the admixture was then refluxed with heat for 23 hours. The reaction mixture was treated in the same manner as described in Example 122 to obtain 262 mg of the title compound (yield: 45%).

25 $^1\text{H-NMR}$ (CDCl₃, 500MHz) : δ 2. 44 (s, 3H), 4. 03 (s, 3H), 4. 06 (s, 3H), 6. 66 (d, J=4. 9Hz, 1H), 7. 27 (d, J=8. 6Hz, 2H), 7. 38 (t, J=7. 3Hz, 1H), 7. 41 (d, J=7. 3Hz, 1H), 7. 46 (s, 1H), 7. 49 (s, 1H), 7. 59 (d, J=7. 3Hz, 1H), 7. 64 (s, 1H), 7. 93 (d, J=8. 6Hz, 2H), 8. 57 (d, J=5. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 399 (M⁺)

Example 134 (Reference Example)

30 4-Hydroxyphenyl 4-nitrophenyl ketone

35 4-Tri-n-butylin-1-methoxymethylphenol (1.282 g) obtained in Example 22 and commercially available 4-nitrobenzoyl chloride (557 mg) were dissolved in chloroform (5 ml), commercially available bis(triphenylphosphine)palladium(II) chloride (8 mg) was added, and the admixture was refluxed with heat for 23 hours. The reaction mixture was partitioned in the same manner as described in Example 23, and the resulting ether layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue (1.047 g) was dissolved in tetrahydrofuran (4 ml), water (5 ml) and 6 N aqueous hydrochloric acid (15 ml) were added, and the admixture was refluxed with heat overnight. The reaction mixture was treated in the same manner as described in Example 123 to obtain 398 mg of the title compound (yield: 55%).

40 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 6. 92 (d, J=8. 6Hz, 2H), 7. 69 (d, J=8. 6Hz, 2H), 7. 89 (d, J=8. 5Hz, 2H), 8. 36 (d, J=8. 5Hz, 2H), 10. 62 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 243 (M⁺)

45 Example 135

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(4-nitrophenyl)methanone [184]

50 Under argon, 4-hydroxyphenyl 4-nitrophenyl ketone (370 mg) obtained in Example 134 and 4-dimethylaminopyridine (204 mg) were added to xylene (5 ml), and the admixture was stirred at room temperature for 1 hour. 4-Chloro-6,7-dimethoxyquinoline (340 mg) was added, and the mixture was then refluxed with heat for 23 hours. The reaction mixture was treated in the same manner as described in Example 130 to obtain 238 mg of the title compound (yield: 36%).

55 $^1\text{H-NMR}$ (CDCl₃, 500MHz) : δ 4. 03 (s, 3H), 4. 07 (s, 3H), 6. 69 (d, J=4. 9Hz, 1H), 7. 29 (d, J=8. 5Hz, 2H), 7. 44 (s, 1H), 7. 47 (s, 1H), 7. 93 (d, J=9. 2Hz, 2H), 7. 96 (d, J=8. 5Hz, 2H), 8. 37 (d, J=8. 5Hz, 2H), 8. 60 (d, J=5. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 430 (M⁺)

Example 136 (Reference Example)

4-Hydroxyphenyl 3,4-methylenedioxyphenyl ketone

5 4-Tri-n-butylin-1-methoxymethylphenol (1.282 g) obtained in Example 22 and commercially available piperonyloyl chloride (664 mg) were dissolved in chloroform (5 ml), commercially available bis(triphenylphosphine)palladium(II) chloride (8 mg) was added, and the admixture was refluxed with heat overnight. The reaction mixture was partitioned in the same manner as described in Example 23, and the resulting ether layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue (1.030 g) was dissolved in tetrahydrofuran (2 ml), water (5 ml) and 6 N aqueous hydrochloric acid (12 ml) were added, and the admixture was refluxed with heat 10.5 hours. The reaction mixture was treated in the same manner as described in Example 123 to obtain 212 mg of the title compound (yield: 29%).

10 ¹H-NMR (DMSO-d₆, 500MHz) : δ 6. 15 (s, 2H), 6. 88 (d, J=8. 6Hz, 2H), 7. 04 (d, J=7. 9Hz, 1H), 7. 21 (d, J=1. 2Hz, 1H), 7. 24 (dd, J=1. 8, 7. 9Hz, 1H), 7. 62 (d, J=9. 2Hz, 2H), 10. 34 (s, 1H)
 15 Mass spectrometry data (FD-MS, m/z) : 242 (M⁺)

Example 137

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(3,4-methylenedioxyphenyl)methanone [185]

20 Under argon, 4-hydroxyphenyl 3,4-methylenedioxyphenyl ketone (202 mg) obtained in Example 136 and 4-dimethylaminopyridine (112 mg) were added to xylene (2 ml), and the admixture was stirred at room temperature for 1 hour. 4-Chloro-6,7-dimethoxyquinoline (187 mg) was added, and the admixture was refluxed with heat for 20 hours. The reaction mixture was treated in the same manner as described in Example 124 to obtain 135 mg of the title compound (yield: 38%).

25 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 04 (s, 3H), 4. 06 (s, 3H), 6. 09 (s, 2H), 6. 64 (d, J=4. 9Hz, 1H), 6. 89 (d, J=7. 9Hz, 1H), 7. 26 (d, J=8. 5Hz, 2H), 7. 38 (d, J=1. 8Hz, 1H), 7. 41 (dd, J=1. 8, 7. 9Hz, 1H), 7. 46 (s, 1H), 7. 49 (s, 1H), 7. 88 (d, J=8. 5Hz, 2H), 8. 57 (d, J=4. 9Hz, 1H)
 30 Mass spectrometry data (FD-MS, m/z) : 429 (M⁺)

Example 138 (Reference Example)

3-Trifluoromethylphenyl 4-methoxyphenyl ketone

35 To commercially available nitromethane (10 ml) were added commercially available anisole (1.081 g), commercially available 3-(trifluoromethyl)benzoyl chloride (2.086 g) and commercially available ytterbium(III) trifluoromethanesulfonate (620 mg), and the admixture was stirred at 60 °C overnight. The reaction mixture was treated in the same manner as described in Example 120 to obtain 719 mg of the title compound (yield: 26%).

40 ¹H-NMR (CDCl₃, 500MHz) : δ 3. 91 (s, 3H), 6. 99 (d, J=9. 2Hz, 2H), 7. 60~7. 64 (m, 1H), 7. 80~7. 83 (m, 1H), 7. 82 (d, J=8. 5Hz, 2H), 7. 93~7. 94 (m, 1H), 8. 01 (s, 1H)
 45 Mass spectrometry data (FD-MS, m/z) : 280 (M⁺)

Example 139 (Reference Example)

3-Trifluoromethylphenyl 4-hydroxyphenyl ketone

50 3-Trifluoromethylphenyl 4-methoxyphenyl ketone (657 mg) obtained in Example 138 was dissolved in N,N-dimethylformamide (35 ml), sodium thiometoxide (411 ml) was added, and the admixture was refluxed with heat under argon for 7 hours. The reaction mixture was treated in the same manner as described in Example 33 to obtain 454 mg of the title compound (yield: 73%).

55 ¹H-NMR (CDCl₃, 500MHz) : δ 5. 85 (s, 1H), 6. 94 (d, J=9. 2Hz, 2H), 7. 62 (t, J=7. 3Hz, 1H), 7. 78 (d, J=9. 2Hz, 2H), 7. 83 (d, J=7. 3Hz, 1H), 7. 93 (d, J=7. 3Hz, 1H), 8. 01 (s, 1H)

Example 140

(3-Trifluoromethylphenyl)[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]methanone [186]

5 Under argon, 3-trifluoromethylphenyl 4-hydroxyphenyl ketone (432 mg) obtained in Example 139 and 4-chloro-6,7-dimethoxyquinoline (363 mg) were dissolved in diethylene glycol dimethyl ether (10 ml), and the solution was then refluxed at 160 °C for 11 hours. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate and then by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1) to obtain 204 mg of the title compound (yield: 28%).

10 1H-NMR (CDCl₃, 500MHz) : δ 4.03 (s, 3H), 4.07 (s, 3H), 6.69 (d, J=4.9Hz, 1H), 7.30 (d, J=9.2Hz, 2H), 7.47 (s, 2H), 7.66 (t, J=7.9Hz, 1H), 7.87 (d, J=7.9Hz, 1H), 7.92 (d, J=9.2Hz, 2H), 8.00 (d, J=7.9Hz, 1H), 8.08 (s, 1H), 8.60 (d, J=4.9Hz, 1H)

15 Mass spectrometry data (FD-MS, m/z) : 453 (M⁺)

Example 141 (Reference Example)

4-Cyclohexylcarbonyl-1-methoxybenzene

20 To commercially available nitromethane (5 ml) were added commercially available anisole (0.5 ml), commercially available cyclohexanecarbonyl chloride (0.63 ml) and commercially available ytterbium(III) trifluoromethanesulfonate (288 mg), and the admixture was stirred at 60 °C for 3 hours. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was washed with saturated aqueous sodium hydrogen carbonate and brine and then dried with anhydrous sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with chloroform to obtain 517 mg of the title compound (yield: 51%).

25 30 1H-NMR (CDCl₃, 500MHz) : δ 1.21~1.88 (m, 10H), 3.19~3.25 (m, 1H), 3.87 (s, 3H), 6.93 (d, J=9.2Hz, 2H), 7.94 (d, J=9.2Hz, 2H)

Mass spectrometry data (FAB-MS, m/z) : 219 (M⁺⁺¹)

Example 142 (Reference Example)

4-Cyclohexylcarbonyl-1-hydroxybenzene

35 40 4-Cyclohexylcarbonyl-1-methoxybenzene (517 mg) obtained in Example 141 was dissolved in N,N-dimethylformamide (20 ml), sodium thiomethoxide (538 mg) was added, and the admixture was refluxed with heat for 1 hour under argon. The reaction mixture was partitioned between water and ethyl acetate, and the ethyl acetate layer was washed with brine and then dried with anhydrous sodium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/acetone to obtain 487 mg of the title compound (yield: 93%).

45 1H-NMR (CDCl₃, 500MHz) : δ 1.23~1.88 (m, 10H), 3.19~3.25 (m, 1H), 6.06 (brs, 1H), 6.89 (d, J=8.6Hz, 2H), 7.90 (d, J=8.6Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 204 (M⁺)

Example 143

4-Cyclohexylcarbonyl-1-[(6,7-dimethoxy-4-quinolyl)oxy]benzene [187]

50 55 Under argon, 4-cyclohexylcarbonyl-1-hydroxybenzene (273 mg) obtained in Example 142 and 4-chloro-6,7-dimethoxyquinoline (100 mg) were dissolved in diethylene glycol dimethyl ether (0.2 ml), and the solution was refluxed at 160 °C for 30 minutes. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was washed with brine and then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/acetone and then with chloroform/methanol to obtain 58 mg of the title compound (yield: 33%).

¹H-NMR (CDCl₃, 500MHz) : δ 1.21~1.93 (m, 10H), 3.24~3.29 (m, 1H), 4.03 (s, 3H), 4.06 (s, 3H), 6.60 (d, J=5.5Hz, 1H), 7.24 (d, J=8.5Hz, 2H), 7.45 (s, 1H), 7.47 (s, 1H), 8.05 (d, J=8.5Hz, 2H), 8.55 (d, J=5.5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 392 (M⁺+1)

5 Example 144 (Reference Example)

2-Trifluoromethylphenyl 4-methoxyphenyl ketone

To commercially available nitromethane (10 ml) were added commercially available anisole (1.081 g), commercially available 2-(trifluoromethyl)benzoyl chloride (2.086 g) and commercially available ytterbium(III) trifluoromethanesulfonate (620 mg), and the admixture was stirred at 60 °C for 6 hours. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate to obtain 1.402 g of the title compound (yield: 50%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 3.88 (s, 3H), 6.93 (d, J=9.2Hz, 2H), 7.37~7.39 (m, 1H), 7.60~7.63 (m, 2H), 7.75 (d, J=9.2Hz, 2H), 7.78 (m, 1H)
 Mass spectrometry data (FD-MS, m/z) : 280 (M⁺)

20 Example 145 (Reference Example)

2-Trifluoromethylphenyl 4-hydroxyphenyl ketone

25 2-Trifluoromethylphenyl 4-methoxyphenyl ketone (1.402 g) obtained in Example 144 was dissolved in N,N-dimethylformamide (15 ml), sodium thiometoxide (877 mg) was added, and the admixture was refluxed with heat for 4 hours under argon. The reaction mixture was treated in the same manner as described in Example 33 to obtain 1.050 g of the title compound (yield: 79%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 5.88 (s, 1H), 6.87 (d, J=8.5Hz, 2H), 7.37~7.38 (m, 1H), 7.58~7.63 (m, 2H), 7.71 (d, J=9.2Hz, 2H), 7.76~7.78 (m, 1H)
 Mass spectrometry data (FD-MS, m/z) : 266 (M⁺)

Example 146

35 (2-Trifluoromethylphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone [35]

Under argon, 2-trifluoromethylphenyl 4-hydroxyphenyl ketone (959 mg) obtained in Example 145 and 4-dimethylaminopyridine (484 mg) were added to xylene (7 ml), and the admixture was stirred at room temperature for 1 hour. 4-Chloro-6,7-dimethoxyquinoline (805 mg) was added, and the admixture was then refluxed with heat overnight. The reaction mixture was treated in the same manner as described in Example 130 to obtain 899 mg of the title compound (yield: 55%).

40 ¹H-NMR (CDCl₃, 500MHz) : δ 4.01 (s, 3H), 4.06 (s, 3H), 6.67 (d, J=5.5Hz, 1H), 7.22 (d, J=9.2Hz, 2H), 7.42 (s, 1H), 7.42~7.44 (m, 1H), 7.45 (s, 1H), 7.62~7.68 (m, 2H), 7.80~7.81 (m, 1H), 7.87 (d, J=8.6Hz, 2H), 8.58 (d, J=5.5Hz, 1H)
 45 Mass spectrometry data (FD-MS, m/z) : 453 (M⁺)

Example 147 (Reference Example)

50 4-n-Butylphenyl 4-methoxyphenyl ketone

To commercially available nitromethane (10 ml) were added commercially available anisole (1.081 g), commercially available 4-(n-butyl)benzoyl chloride (1.967 g) and commercially available ytterbium(III) trifluoromethanesulfonate (620 mg), and the admixture was stirred at 60 °C for 6 hours. The reaction mixture was treated in the same manner as described in Example 120 to obtain 863 mg of the title compound (yield: 32%).

¹H-NMR (CDCl₃, 500MHz) : δ 0.95 (t, J=7.3Hz, 3H), 1.38 (tq, J=7.3, 7.3Hz, 2H), 1.64 (quint, J=7.3Hz, 2H), 2.69 (t, J=7.3Hz, 2H), 3.89 (s, 3H), 6.96 (d, J=9.2Hz, 2H), 7.27 (d, J=8.6Hz, 2H), 7.69 (d, J=8.6Hz, 2H), 7.82

(d, J=9. 2Hz, 2H)

Mass spectrometry data (FD-MS, m/z) : 268 (M⁺)

Example 148 (Reference Example)

5

4-n-Butylphenyl 4-hydroxyphenyl ketone

10 4-n-Butylphenyl 4-methoxyphenyl ketone (863 mg) obtained in Example 147 was dissolved in N,N-dimethylformamide (50 ml), sodium thiomethoxide (563 mg) was added, and the admixture was refluxed with heat for 7 hours under argon. The reaction mixture was treated in the same manner as described in Example 33 to obtain 787 mg of the title compound (yield: 96%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 0. 95 (t, J=7. 3Hz, 3H), 1. 38 (tq, J=7. 3, 7. 3Hz, 2H), 1. 64 (septet, J=7. 3Hz, 2H), 2. 69 (t, J=7. 9Hz, 2H), 6. 35 (s, 1H), 6. 92 (d, J=8. 5, 2H), 7. 28 (d, J=7. 9Hz, 2H), 7. 69 (d, J=8. 6Hz, 2H), 7. 77 (d, J=8. 5Hz, 2H)

Mass spectrometry data (FD-MS, m/z) : 254 (M⁺)

Example 149

20 (4-n-Butylphenyl){4-[6,7-dimethoxy-4-quinolyl]oxy}phenyl]methanone [40]

25 Under argon, 4-n-butylphenyl 4-hydroxyphenyl ketone (727 mg) obtained in Example 148 and 4-chloro-6,7-dimethoxyquinoline (639 mg) were dissolved in diethylene glycol dimethyl ether (10 ml), and the solution was then refluxed with heat at 180 °C for 10 hours. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate and then with chloroform, followed by chromatography on silica gel eluting with hexane/acetone to obtain 400 mg of the title compound (yield: 32%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 0. 95 (t, J=7. 3Hz, 3H), 1. 38 (tq, J=7. 3, 7. 3Hz, 2H), 1. 62~1. 68 (m, 2H), 2. 71 (t, J=7. 3Hz, 2H), 4. 04 (s, 3H), 4. 07 (s, 3H), 6. 65 (d, J=4. 9Hz, 1H), 7. 26 (d, J=8. 5Hz, 2H), 7. 31 (d, J=7. 9Hz, 2H), 7. 46 (s, 1H), 7. 49 (s, 1H), 7. 76 (d, J=7. 9Hz, 2H), 7. 92 (d, J=8. 5Hz, 2H), 8. 58 (d, J=5. 5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 440 (M⁺-1)

35 Example 150 (Reference Example)

3-Fluorophenyl 4-methoxyphenyl ketone

40 To commercially available nitromethane (5 ml) were added commercially available anisole (541 mg), commercially available 3-fluorobenzoyl chloride (793 mg) and commercially available scandium(III) trifluoromethanesulfonate (49 mg), and the admixture was stirred at 60 °C for 3 days. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/acetone to obtain 585 mg of the title compound (yield: 51%).

45

Mass spectrometry data (FAB-MS, m/z) : 231 (M⁺+1)

Example 151 (Reference Example)

50 4-Hydroxyphenyl 3-fluorophenyl ketone

55 3-Fluorophenyl 4-methoxyphenyl ketone (580 mg) obtained in Example 150 was dissolved in dichloromethane (5 ml), a solution of 1.0 M boron tribromide in dichloromethane (23 ml) was added while cooled in ice, and the admixture was stirred at room temperature for 3 days. The reaction mixture was treated in the same manner as described in 121 to obtain 402 mg of the title compound (yield: 74%).

1H-NMR (DMSO-d₆, 500MHz) : δ 6. 91 (d, J=8. 5Hz, 2H), 7. 44~7. 49 (m, 3H), 7. 57~7. 61 (m, 1H), 7. 68 (d, J=8. 5Hz, 2H), 10. 51 (brs, 1H)

Mass spectrometry data (FAB-MS, m/z) : 217 (M⁺+1)

Example 152

5 {4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(3-fluorophenyl)methanone [176]

Under argon, 4-hydroxyphenyl 3-fluorophenyl ketone (373 mg) obtained in Example 151 and 4-dimethylaminopyridine (232 mg) were added to xylene (5 ml), and the admixture was stirred at room temperature for 3 hours. 4-Chloro-6,7-dimethoxyquinoline (386 mg) was added, and the mixture was then refluxed with heat for 21 hours. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/acetone and then with chloroform, followed by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1), to obtain 484 mg of the title compound (yield: 70%).

15

¹H-NMR (CDCl₃, 500MHz) : δ 4.04 (s, 3H), 4.07 (s, 3H), 6.67 (d, J=4.9Hz, 1H), 7.28 (d, J=7.9Hz, 2H), 7.31~7.33 (m, 1H), 7.46 (s, 1H), 7.47 (s, 1H), 7.48~7.53 (m, 2H), 7.59~7.61 (m, 1H), 7.93 (d, J=8.6Hz, 2H), 8.59 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 403 (M⁺)

20

Example 153

25 N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2-methoxyphenyl)urea [113]

6,7-Dimethoxy-4-(4-aminophenoxy)quinazoline (100 mg) was dissolved in toluene (10 ml) with heat, 2-methoxyphenyl isocyanate (0.36 ml) was added, and the admixture was refluxed with heat for 40 minutes. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) and then with chloroform/acetone (5/1) to obtain 112 mg of the title compound (yield: 75%).

30

¹H-NMR (DMSO-d₆, 500MHz) : δ 3.90 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.90 (t, J=7.9Hz, 1H), 6.96 (t, J=7.9Hz, 1H), 7.03 (t, J=7.9Hz, 1H), 7.23 (d, J=9.2Hz, 2H), 7.39 (s, 1H), 7.55 (d, J=9.2Hz, 2H), 7.57 (s, 1H), 8.15 (d, J=7.9Hz, 1H), 8.25 (s, 1H), 8.55 (s, 1H), 9.44 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 446 (M⁺)

40

N-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(3-methoxyphenyl)urea [114]

45

6,7-Dimethoxy-4-(4-aminophenoxy)quinazoline (100 mg) was dissolved in toluene (10 ml) with heat, 3-methoxyphenyl isocyanate (0.36 ml) was added, and the admixture was refluxed with heat for 40 minutes. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) and then with chloroform/acetone (5/1) to obtain 31 mg of the title compound (yield: 21%).

50

¹H-NMR (DMSO-d₆, 500MHz) : δ 3.74 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.56 (d, J=7.9Hz, 1H), 6.96 (d, J=7.9Hz, 1H), 7.15~7.25 (m, 4H), 7.38 (s, 1H), 7.53~7.60 (m, 3H), 8.55 (s, 1H), 8.76 (s, 1H), 8.81 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 446 (M⁺)

55

Example 155

5 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(4-methoxyphenyl)urea [99]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinazoline (81 mg) was dissolved in toluene (5 ml) with heat, 4-methoxyphenyl isocyanate (0.29 ml) was added, and the admixture was refluxed with heat for 40 minutes. The separated solid was filtered and washed with toluene to obtain 60 mg of the title compound (yield: 49%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 3. 79 (s, 3H), 4. 06 (s, 3H), 4. 07 (s, 3H), 6. 48 (s, 1H), 6. 64 (s, 1H), 6. 91 (d, J=9. 2Hz, 2H), 7. 20 (d, J=8. 6Hz, 2H), 7. 27 (d, J=8. 6Hz, 2H), 7. 32 (s, 1H), 7. 47 (d, J=9. 2Hz, 2H), 7. 55 (s, 1H), 8. 60 (s, 1H)

15 Mass spectrometry data (FAB-MS, m/z) : 447 (M⁺+1)

Example 156

20 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(2-fluorophenyl)urea [116]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinazoline (100 mg) was dissolved in toluene (10 ml) with heat, 2-fluorophenyl isocyanate (0.30 ml) was added, and the admixture was refluxed with heat for 40 minutes. The separated solid was filtered and washed with toluene to obtain 96 mg of the title compound (yield: 66%).

30 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 98 (s, 3H), 3. 99 (s, 3H), 7. 00~7. 04 (m, 1H), 7. 13~7. 17 (m, 1H), 7. 23~7. 27 (m, 3H), 7. 39 (s, 1H), 7. 54~7. 57 (m, 3H), 8. 10~8. 20 (m, 1H), 8. 55 (s, 1H), 8. 65 (s, 1H), 9. 26 (s, 1H)

30 Mass spectrometry data (FD-MS, m/z) : 434 (M⁺)

Example 157

35 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-n-butylurea [220]

40 6,7-Dimethoxy-4-(4-aminophenoxy)quinazoline (100 mg) was dissolved in toluene (10 ml) with heat, n-butyl isocyanate (0.29 ml) was added, and the admixture was refluxed with heat for 40 minutes. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (5/1) to obtain 75 mg of the title compound (yield: 56%).

45 ¹H-NMR (DMSO-d₆, 500MHz) : δ 0. 90 (t, J=7. 3Hz, 3H), 1. 28~1. 46 (m, 4H), 3. 09 (q, J=6. 7Hz, 2H), 3. 97 (s, 3H), 3. 99 (s, 3H), 6. 23 (brs, 1H), 7. 14 (d, J=9. 2Hz, 2H), 7. 37 (s, 1H), 7. 47 (d, J=9. 2Hz, 2H), 7. 55 (s, 1H), 8. 53 (s, 1H), 8. 58 (brs, 1H)

50 Mass spectrometry data (FD-MS, m/z) : 396 (M⁺)

Example 158

N-[4-[6,7-Dimethoxy-4-quinolyl]oxy]phenyl)-(4-tert-butylphenyl)carboxamide [213]

55 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) and commercially available 4-tert-butylbenzoic acid (102 mg) were dissolved in N,N-dimethylformamide (3 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (106 mg) was added, and the admixture was stirred at room temperature for 6 hours, after which the reaction mixture was purified in the same manner as described in Example 51 to obtain 29 mg of the title compound (yield: 35%).

¹H-NMR (CDCl₃, 90MHz) : δ 1.36 (s, 9H), 4.05 (s, 3H), 4.08 (s, 3H), 6.48 (d, J=5.3Hz, 1H), 7.1~8.1 (m, 11H), 8.49 (d, J=5.3Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 456 (M⁺)

5. Example 159

N-[4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl]-N-methyl-(4-t-butylphenyl)carboxamide [156]

N-[4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl]-N-methyl-(4-t-butylphenyl)carboxamide (100 mg) obtained in Example 158 was dissolved in N,N-dimethylformamide (3 ml), sodium hydride (10 mg) was added, and the admixture was stirred at 0 °C for 1 hour, methyl iodide (31 mg) was added, and the admixture was stirred for a further 3 hours. The reaction mixture was purified in the same manner as described in Example 51 to obtain 48 mg of the title compound (yield: 46%).

¹H-NMR (CDCl₃, 90MHz) : δ 1.28 (s, 9H), 3.54 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.32 (d, J=5.3Hz, 1H), 7.0~7.3 (m, 8H), 7.42 (s, 1H), 7.50 (s, 1H), 8.47 (d, J=5.3Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 470 (M⁺)

Example 160

20 N-(4-t-Butylphenyl)-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]carboxamide [155]

4-[6,7-Dimethoxy-4-quinolyl]oxybenzoic acid (54 mg) and commercially available 4-tert-butylaniline (102 mg) were dissolved in N,N-dimethylformamide (3 ml), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (106 mg) was added, and the admixture was stirred at room temperature for 6 hours, after which the reaction mixture was purified in the same manner as described in Example 51 to obtain 29 mg of the title compound (yield: 35%).

¹H-NMR (CDCl₃, 90MHz) : δ 1.34 (s, 9H), 4.03 (s, 3H), 4.06 (s, 3H), 6.57 (d, J=5.3Hz, 1H), 7.2~8.1 (m, 11H), 8.55 (d, J=5.3Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 456 (M⁺)

30 Example 161 (Reference Example)

2-(6,7-Dimethoxy-4-quinolyl)-2-(4-bromophenyl)acetonitrile

35 Commercially available 4-bromophenylacetonitrile (4.3 g) was dissolved in toluene (10 ml) and the temperature was lowered to 0 °C, after which sodium hydride (1.0 g) was added, the temperature was raised to 50 °C, and the admixture was then stirred for 1 hour. Next, 6,7-dimethoxy-4-chloroquinoline (2.2 g) was added, and the admixture was stirred for 15 hours, after which water was poured and the mixture was extracted with ethyl acetate. After drying with anhydrous sodium sulfate and removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (2/1) to obtain 850 mg of the title compound (yield: 22%).

¹H-NMR (CDCl₃, 90MHz) : δ 3.66 (s, 3H), 3.80 (s, 3H), 5.40 (s, 1H), 6.74 (s, 1H), 6.9~7.4 (m, 6H), 8.54 (d, J=4.6Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 382 (M⁺), 384 (M⁺+2)

45 Example 162 (Reference Example)

6,7-Dimethoxy-4-(4-bromophenylmethyl)quinoline

50 2-(6,7-Dimethoxy-4-quinolyl)-2-(4-bromophenyl)acetonitrile (850 mg) obtained in Example 161 was dissolved in 60% aqueous sulfuric acid (5 ml), and the solution was refluxed with heat for 1 hour and then poured into a container with ice and aqueous ammonia. The solution was neutralized with hydrochloric acid and extracted with methylene chloride. After drying with anhydrous sodium sulfate and removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 260 mg of the title compound (yield: 33%).

¹H-NMR (CDCl₃, 90MHz) : δ 3.90 (s, 3H), 4.02 (s, 3H), 4.31 (s, 2H), 6.9~7.5 (m, 7H), 8.63 (d, J=4.4Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 357 (M⁺), 359 (M⁺+2)

Example 163 (Reference Example)

6,7-Dimethoxy-4-(4-tri-n-butylstanniophenylmethyl)quinoline

5 Under argon, 6,7-dimethoxy-4-(4-bromophenylmethyl)quinoline (250 mg) obtained in Example 162 was dissolved in tetrahydrofuran (4 ml), and the solution was cooled to -78 °C, a solution of 2.5 M n-butylolithium in hexane (0.3 ml) was added dropwise, and the admixture was stirred for 1 hour. An solution of tri-n-butyltin chloride in tetrahydrofuran (1 ml) was then added dropwise, and the admixture was stirred at -78 °C for 2 hours. After adding water, extracting with ethyl acetate and drying with anhydrous sodium sulfate, the solvent was removed by distillation, and the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (3/1) to obtain 85 mg of the title compound (yield: 22%).

10 ¹H-NMR (CDCl₃, 90MHz) : δ 0. 7~1. 6 (m, 27H), 3. 88 (s, 3H), 4. 02 (s, 3H), 4. 34 (s, 2H), 7. 0~7. 5 (m, 7H), 8. 63 (d, J=4. 6Hz, 1H)

15 Example 164

(4-[(6,7-Dimethoxy-4-quinolyl)methyl]phenyl)(4-t-butylphenyl)methanone [162]

20 6,7-Dimethoxy-4-(4-tri-n-butylstanniophenylmethyl)quinoline (82 mg) obtained in Example 162, commercially available 4-t-butylbenzoyl chloride (31 mg) and a catalytic amount of commercially available bis(triphenylphosphine)palladium(II) chloride were dissolved in chloroform (3 ml), and the admixture was stirred for 15 hours under reflux with heat. After the addition of water, the admixture was extracted with methylene chloride, and the organic layer was washed with brine and saturated aqueous potassium fluoride and then dried with anhydrous sodium sulfate. After removing the solvent by distillation, the resulting residue was purified by thin layer chromatography on silica gel eluting with hexane/ethyl acetate (2/1) to obtain 6 mg of the title compound (yield: 10%).

25 ¹H-NMR (CDCl₃, 90MHz) : δ 1. 36 (s, 9H), 3. 91 (s, 3H), 4. 03 (s, 3H), 4. 45 (s, 2H), 7. 0~7. 9 (m, 11H), 8. 66 (d, J=4. 4Hz, 1H)

30 Mass spectrometry data (FAB-MS, m/z) : 440 (M⁺+1)

Example 165

N-(4-Fluorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)thiourea [203]

35 40 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (100 mg) was dissolved in toluene (10 ml) with heat, 4-fluorophenylthio isocyanate (52 mg) was added, and the admixture was refluxed with heat for 24 hours. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 32 mg of the title compound (yield: 21%).

45 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 93 (s, 3H), 3. 95 (s, 3H), 6. 50 (d, J=4. 9Hz, 1H), 7. 15~7. 25 (m, 4H), 7. 40 (S, 1H), 7. 47~7. 50 (m, 3H), 7. 59 (d, J=8. 6Hz, 2H), 8. 50 (d, J=5. 5Hz, 1H), 9. 80 (brs, 1H), 9. 84 (brs, 1H)
Mass spectrometry data (FAB-MS, m/z) : 450 (M⁺+1)

Example 166

1-(4-Fluorophenyl)-2-cyano-3-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]guanidine [204]

50 55 N-(4-Fluorophenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}thiourea (33 mg) obtained in Example 165, dicyclohexylcarbodiimide (31 mg) and a catalytic amount of diisopropylethyl amine were dissolved in methylene chloride (10 ml). To this solution, a solution of cyanamide (16 mg) in THF (1 ml) was added, and the admixture was stirred at room temperature overnight. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 34 mg of the title compound (yield: 99%).

¹H-NMR (CDCl₃, 90MHz) : δ 4.03 (s, 3H), 4.05 (s, 3H), 6.50 (d, J=5. 1Hz, 1H), 6.8~7.6 (m, 10H), 8.52 (d, J=5. 3Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 457 (M⁺)

5 Example 167

N - (2 - F l u o r o p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
q u i n o l y l) o x y] p h e n y l } t h i o u r e a [2 0 5]

10

15 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (100 mg) was dissolved in toluene (10 ml) with heat, 2-fluorophenylthio isocyanate (0.05 ml) was added, and the admixture was refluxed with heat for 24 hours. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 66 mg of the title compound (yield: 42%).

19 ¹H-NMR (CDCl₃, 90MHz) : δ 4.03 (s, 3H), 4.05 (s, 3H), 6.53 (d, J=5. 3Hz, 1H), 7.1~8.0 (m, 10H), 8.53 (d, J=5. 1Hz, 1H)
 20 Mass spectrometry data (FAB-MS, m/z) : 450 (M⁺+1)

Example 168

1 - (2 - F l u o r o p h e n y l) - 2 - c y a n o - 3 - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
q u i n o l y l) o x y] p h e n y l } q u a n i d i n e [2 0 6]

25

30 N-(2-Fluorophenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}thiourea (42 mg) obtained in Example 167, dicyclohexylcarbodiimide (37 mg) and a catalytic amount of diisopropylethyl amine were dissolved in methylene chloride (10 ml). To this solution, a solution of cyanamide (20 mg) in THF (1 ml) was added, and the admixture was stirred at room temperature overnight. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 41 mg of the title compound (yield: 99%).

35 ¹H-NMR (CDCl₃, 90MHz) : δ 4.04 (s, 3H), 4.06 (s, 3H), 6.53 (d, J=5. 3Hz, 1H), 7.1~7.6 (m, 10H), 8.47 (d, J=5. 3Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 457 (M⁺)

35

Example 169

N - (2 - M e t h o x y p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
q u i n o l y l) o x y] p h e n y l } t h i o u r e a [2 0 7]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (100 mg) was dissolved in toluene (10 ml) with heat, 2-methoxyphenylthio isocyanate (0.05 ml) was added, and the admixture was refluxed with heat for 24 hours. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 78 mg of the title compound (yield: 50%).

50 ¹H-NMR (CDCl₃, 90MHz) : δ 3.86 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.52 (d, J=5. 3Hz, 1H), 6.9~8.1 (m, 10H), 8.52 (d, J=5. 1Hz, 1H)
 Mass spectrometry data (FAB-MS, m/z) : 462 (M⁺+1)

55

Example 170

5 N - (2 - M e t h y l p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
quinolyl)oxy]phenyl}thiourea [209]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (80 mg) was dissolved in toluene (10 ml) with heat, 2-methylphenylthio isocyanate (0.04 ml) was added, and the admixture was refluxed with heat for 24 hours. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 31 mg of the title compound (yield: 26%).

15 ¹H-NMR (CDCl₃, 90MHz) : δ 2. 38 (s, 3H), 4. 03 (s, 3H), 4. 04 (s, 3H), 6. 50 (d, J=5. 3Hz, 1H), 7. 1~7. 8 (m, 10H),
Mass spectrometry data (FD-MS, m/z) : 445 (M⁺)

Example 171

20 N - (3 - M e t h y l p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
quinolyl)oxy]phenyl}thiourea [211]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (81 mg) was dissolved in toluene (10 ml) with heat, 3-methylphenylthio isocyanate (0.04 ml) was added, and the admixture was refluxed with heat for 15 minutes. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 66 mg of the title compound (yield: 55%).

30 ¹H-NMR (CDCl₃, 90MHz) : δ 2. 40 (s, 3H), 4. 03 (s, 3H), 4. 05 (s, 3H), 6. 52 (d, J=5. 1Hz, 1H), 7. 1~7. 8 (m, 10H),
8. 51 (d, J=5. 3Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 445 (M⁺)

Example 172

35 1-(2-Methylphenyl)-2-cyano-3-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]guanidine [210]

40 N-(2-Methylphenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}thiourea (24 mg) obtained in Example 170, dicyclohexylcarbodiimide (45 mg) and a catalytic amount of diisopropylethyl amine were dissolved in methylene chloride (7 ml), to which a solution of cyanamide (28 mg) in THF (1 ml) was added, and the admixture was stirred at room temperature overnight. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 18 mg of the title compound (yield: 76%).

45 ¹H-NMR (CDCl₃, 500MHz) : δ 2. 36 (s, 3H), 4. 03 (s, 3H), 4. 04 (s, 3H), 6. 46 (d, J=5. 5Hz, 1H), 7. 30~7. 45 (m, 9H), 7. 50 (s, 1H), 8. 49 (d, J=4. 9Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 453 (M⁺)

Example 173

50 1-(3-Methylphenyl)-2-cyano-3-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]guanidine [212]

55 N-(3-Methylphenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}thiourea (18 mg) obtained in Example 171, dicyclohexylcarbodiimide (35 mg) and a catalytic amount of diisopropylethyl amine were dissolved in methylene chloride (6 ml), to which a solution of cyanamide (23 mg) in THF (1 ml) was added, and the admixture was stirred at room temperature overnight. After removing the solvent by distillation, the resulting residue was purified by column chromatography on silica gel eluting with chloroform/methanol (100/1) to obtain 19 mg of the title compound (yield: 95%).

¹H-NMR (CDCl₃, 500MHz) : δ 2. 38 (s, 3H), 4. 03 (s, 3H), 4. 04 (s, 3H), 6. 48 (d, J=5. 5Hz, 1H), 7. 10~7. 45 (m,

9H), 7. 51 (s, 1H), 8. 48 (d, J=5. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 453 (M⁺)

Example 174

5

4-Hydroxyphenyl 3-trifluoroxypyhenyl ketone (Reference Example)

10

4-Tri-n-butylin-1-methoxymethylphenol (1.3 g) obtained in Example 22 and commercially available 4-(trifluoromethoxy)benzoyl chlorobenzoyl chloride (674 mg) were dissolved in chloroform (5 ml), commercially available bis(triphenylphosphine)palladium(II) chloride (8 mg) was added, and the admixture was refluxed overnight. The reaction mixture was partitioned in the same manner as described in Example 23, and the ether layer was dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue (2.0 g) was dissolved in tetrahydrofuran (4 ml), water (5 ml) and 6 N aqueous hydrochloric acid (15 ml) were added, and the admixture was refluxed for 8 hours. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was dried with magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 2.1 g of the title compound.

15

Mass spectrometry data (FD-MS, m/z) : 282 (M⁺)

20

Example 175

(4-Trifluoromethoxyphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone [284]

25

4-Hydroxyphenyl 3-trifluoroxypyhenyl ketone (581 mg) obtained in Example 117 and commercially available 4-dimethylaminopyridine (277 mg) were added to xylene (20 ml), and the admixture was stirred at room temperature under argon. After 1 hour, 4-chloro-6,7-dimethoxyquinoline (460 mg) was added, and the admixture was refluxed with heat for 24 hours. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate and then with chloroform, followed by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1), to obtain 470 mg of the title compound (yield: 49%).

30

¹H-NMR (CDCl₃, 500MHz) : δ 4. 03 (s, 3H), 4. 07 (s, 3H), 6. 66 (d, J=4. 5Hz, 1H), 7. 28 (d, J=8. 5Hz, 2H), 7. 35 (d, J=8. 7Hz, 2H), 7. 46 (s, 1H), 7. 47 (s, 1H), 7. 89 (d, J=8. 5Hz, 2H), 7. 92 (d, J=9. 2Hz, 2H), 8. 59 (d, J=4. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 469 (M⁺)

Example 176

40

4-Methoxyphenyl 4-iodophenyl ketone (Reference Example)

45

To commercially available nitromethane (10 ml) were added commercially available anisole (1.08 g), commercially available 4-iodobenzoyl chloride (2.67 g) and commercially available ytterbium(III) trifluoromethanesulfonate (620 mg), and the admixture was stirred at 60 °C overnight. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 722 mg of the title compound (yield: 21%).

50

Mass spectrometry data (FD-MS, m/z) : 338 (M⁺)

Example 177

4-Hydroxyphenyl 4-iodophenyl ketone (Reference Example)

55

4-Methoxyphenyl 4-iodophenyl ketone (722 mg) obtained in Example 119 was dissolved in dichloromethane (20 ml), a solution of 1.0 M boron tribromide in dichloromethane (9 ml) was added while cooled in ice, and the admixture was stirred at room temperature overnight. The reaction mixture was then poured into ice water and partitioned between water and chloroform. The chloroform layer was dried with anhydrous magnesium sulfate and the solvent was

removed by reduced-pressure distillation. The resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 380 mg of the title compound (yield: 55%).

5 ¹H-NMR (DMSO-d₆, 500MHz) : δ 6. 89 (d, J=8. 6Hz, 2H), 7. 44 (d, J=8. 5Hz, 2H), 7. 65 (d, J=8. 6Hz, 2H), 7. 92 (d, J=8. 5Hz, 2H), 10. 47 (s, 1H)
 Mass spectrometry data (FAB-MS, m/z) : 325 (M⁺+1)

Example 178

10 [4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl](4-iodophenyl)methanone [285]

Under argon, 4-hydroxyphenyl 4-iodophenyl ketone (380 mg) obtained in Example 120 and 4-dimethylaminopyridine (158 mg) were added to xylene (11 ml), and the admixture was stirred at room temperature. After 2 hours, 4-chloro-6,7-dimethoxyquinoline (262 mg) was added, and the admixture was refluxed with heat overnight. The reaction mixture 15 was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate and then with chloroform/ethyl acetate, followed by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1), to obtain 459 mg of the title compound (yield: 77%).

20 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 03 (s, 3H), 4. 07 (s, 3H), 6. 66 (d, J=4. 9Hz, 1H), 7. 27 (d, J=7. 6Hz, 2H), 7. 46 (s, 1H), 7. 47 (s, 1H), 7. 54 (d, J=8. 6Hz, 2H), 7. 88 (d, J=7. 9Hz, 2H), 7. 90 (d, J=8. 6Hz, 2H), 8. 58 (d, J=5. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 511 (M⁺)

25 Example 179

4-Methoxyphenyl 4-bromophenyl ketone (Reference Example)

To commercially available nitromethane (10 ml) were added commercially available anisole (1.08 g), commercially 30 available 4-bromobenzoyl chloride (2.20 g) and commercially available ytterbium(III) trifluoromethanesulfonate (620 mg), and the admixture was stirred at 60 °C overnight. The reaction mixture was partitioned between water and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 1.65 g of the title compound (yield: 57%).

35 ¹H-NMR (CDCl₃, 500MHz) : δ 3. 89 (s, 3H), 6. 97 (d, J=8. 6Hz, 2H), 7. 62 (d, J=1. 8Hz, 2H), 7. 62 (d, J=1. 8Hz, 2H), 7. 80 (d, J=9. 2Hz, 2H)
 Mass spectrometry data (FD-MS, m/z) : 290 (M⁺), 292 (M⁺+2)

40 Example 180

4-Hydroxyphenyl 4-bromophenyl ketone (Reference Example)

4-Methoxyphenyl 4-bromophenyl ketone (1.65 g) obtained in Example 122 was dissolved in dichloromethane (20 45 ml), a solution of 1.0 M boron tribromide in dichloromethane (23 ml) was added while cooled in ice, and the admixture was stirred at room temperature overnight. The reaction mixture was then poured into ice water and partitioned between water and chloroform. The chloroform layer was dried with anhydrous magnesium sulfate and the solvent was removed by reduced-pressure distillation. The resulting residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain 1.34 g of the title compound (yield: 85%).

50 ¹H-NMR (DMSO-d₆, 500MHz) : δ 6. 90 (d, J=8. 5Hz, 2H), 7. 61 (d, J=8. 5Hz, 2H), 7. 66 (d, J=8. 6Hz, 2H), 7. 74 (d, J=8. 5Hz, 2H), 10. 46 (brs, 1H)
 Mass spectrometry data (FD-MS, m/z) : 276 (M⁺), 278 (M⁺+2)

Example 181

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(4-bromophenyl)methanone [286]

5 Under argon, 4-hydroxyphenyl 4-bromophenyl ketone (1.182 g) obtained in Example 123 and 4-dimethylaminopyridine (573 mg) were added to xylene (37 ml), and the admixture was stirred at room temperature. After 30 minutes, 4-chloro-6,7-dimethoxyquinoline (954 mg) was added, and the admixture was refluxed with heat overnight. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified first by chromatography on silica gel eluting with chloroform/ethyl acetate and then by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1) to obtain 1.574 g of the title compound (yield: 79%).

10 1H-NMR (CDCl₃, 500MHz) : δ 4.05 (s, 3H), 4.06 (s, 3H), 6.66 (d, J=4.9Hz, 1H), 7.27 (d, J=8.6Hz, 2H), 7.46 (s, 1H), 7.47 (s, 1H), 7.65 (d, J=7.9Hz, 2H), 7.70 (d, J=8.5Hz, 2H), 7.90 (d, J=8.6Hz, 2H), 8.58 (d, J=5.5Hz, 1H)
 15 Mass spectrometry data (FD-MS, m/z) : 463 (M⁺), 465 (M⁺+2)

Example 182

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}[4-(N-methylpiperazino)phenyl]methanone [287]

20 Under argon, 4-hydroxyphenyl 4-bromophenyl ketone (232 mg) obtained in Example 123 was added to toluene (5 ml), and commercially available N-methylpiperazine (61 mg), sodium t-butoxide (67 mg), bis (triphenylphosphine)palladium(II) chloride (7 mg) were further added, and the admixture was stirred at 100 °C for 17 hours. The reaction mixture was partitioned between brine and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by thin layer chromatography on silica gel eluting with chloroform/methanol (10/1) to obtain 53 mg of the title compound (yield: 22%).

25 1H-NMR (CDCl₃, 500MHz) : δ 2.37 (s, 3H), 2.58 (t, J=5.5Hz, 4H), 3.41 (t, J=5.5Hz, 4H), 4.04 (s, 3H), 4.06 (s, 3H), 6.63 (d, J=4.9Hz, 1H), 6.92 (d, J=9.2Hz, 2H), 7.25 (d, J=8.5Hz, 2H), 7.45 (s, 1H), 7.51 (s, 1H), 7.81 (d, J=8.5Hz, 2H), 7.87 (d, J=8.6Hz, 2H), 8.56 (d, J=4.9Hz, 1H)
 30 Mass spectrometry data (FD-MS, m/z) : 483 (M⁺)

Example 183

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}[4-morpholinophenyl]methanone [288]

35 Under argon, 4-hydroxyphenyl 4-bromophenyl ketone (232 mg) obtained in Example 123 was added to toluene (5 ml), and commercially available morpholine (52 mg), sodium t-butoxide (67 mg), bis (triphenylphosphine)palladium(II) chloride (7 mg) were further added, and the admixture was stirred at 100 °C overnight. The reaction mixture was partitioned between brine and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1) to obtain 32 mg of the title compound (yield: 14%).

40 1H-NMR (CDCl₃, 500MHz) : δ 3.34 (t, J=4.9Hz, 4H), 3.88 (t, J=4.9Hz, 4H), 4.04 (s, 3H), 4.07 (s, 3H), 6.64 (d, J=5.5Hz, 1H), 6.92 (d, J=9.2Hz, 2H), 7.26 (d, J=7.3Hz, 2H), 7.83 (d, J=9.2Hz, 2H), 7.87 (d, J=8.5Hz, 2H), 8.56 (d, J=5.5Hz, 1H), 7.49 (s, 1H), 7.51 (s, 1H)
 45 Mass spectrometry data (FD-MS, m/z) : 470 (M⁺)

50 Example 184

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}[4-pyrrolidinophenyl]methanone [289]

55 Under argon, 4-hydroxyphenyl 4-bromophenyl ketone (232 mg) obtained in Example 123 was added to toluene (5 ml), and commercially available pyrrolidine (43 mg), sodium t-butoxide (67 mg), bis (triphenylphosphine)palladium(II) chloride (7 mg) were further added, and the admixture was stirred at 100 °C overnight. The reaction mixture was partitioned between brine and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by thin layer chromatography

on silica gel eluting with chloroform/ethyl acetate (5/1) to obtain 45 mg of the title compound (yield: 20%).

5 ¹H-NMR (CDCl₃, 500MHz) : δ 2. 05–2. 08 (m, 4H), 3. 38–3. 41 (m, 4H), 4. 04 (s, 3H), 4. 06 (s, 3H), 6. 57 (d, J=9. 2Hz, 2H), 6. 62 (d, J=4. 9Hz, 1H), 7. 24 (d, J=8. 6Hz, 2H), 7. 45 (s, 1H), 7. 52 (s, 1H), 7. 82 (d, J=9. 2Hz, 2H), 7. 84 (d, J=8. 5Hz, 2H), 8. 55 (d, J=4. 9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 454 (M⁺)

Example 185

10 {4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}[4-piperidinophenyl]methanone [290]

Under argon, 4-hydroxyphenyl 4-bromophenyl ketone (232 mg) obtained in Example 123 was added to toluene (5 ml), and commercially available piperidine (51 mg), sodium t-butoxide (67 mg), bis (triphenylphosphine)palladium(II) chloride (7 mg) were further added, and the admixture was stirred at 100 °C overnight. The reaction mixture was partitioned between brine and chloroform, and the chloroform layer was then dried with anhydrous magnesium sulfate. After removing the solvent by reduced-pressure distillation, the resulting residue was purified by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (5/1) to obtain 75 mg of the title compound (yield: 32%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 68 (brs, 6H), 3. 38–3. 39 (m, 4H), 4. 04 (s, 3H), 4. 06 (s, 3H), 6. 63 (d, J=4. 9Hz, 1H), 6. 89 (d, J=8. 6Hz, 2H), 7. 25 (d, J=8. 5Hz, 2H), 7. 45 (s, 1H), 7. 52 (s, 1H), 7. 80 (d, J=9. 2Hz, 2H), 7. 86 (d, J=8. 6Hz, 2H), 8. 56 (d, J=4. 9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 468 (M⁺)

20 Example 186

25 N-(2-Methoxy-4-biphenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea [222]

30

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was suspended in toluene (5 ml), after the addition of triethylamine (1 ml), triphosgene (52 mg) was added, and the admixture was refluxed with heat for 2 minutes. 2-Methoxy-4-biphenylamine (103 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 13 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 89 mg of the title compound (yield: 98%).

35 ¹H-NMR (CDCl₃, 500MHz) : δ 3. 67 (s, 3H), 4. 00 (s, 3H), 4. 04 (s, 3H), 6. 44 (d, J=5. 5Hz, 1H), 6. 86 (d, J=8. 5Hz, 1H), 7. 10 (d, J=8. 6Hz, 2H), 7. 21–7. 37 (m, 4H), 7. 43 (s, 1H), 7. 53–7. 59 (m, 5H), 7. 79 (s, 1H), 8. 41 (s, 1H), 8. 48 (d, J=4. 9Hz, 1H), 8. 53 (d, J=2. 4Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 521 (M⁺)

40 Example 187

45 N-(2,6-Diisopropylphenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea [223]

50

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) was suspended in toluene (5 ml), after the addition of triethylamine (1 ml), triphosgene (53 mg) was added, and the admixture was refluxed with heat for 8 minutes. 2,6-Diisopropylaniline (0.05 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 15 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with

chloroform/acetone (10/1) to obtain 69 mg of the title compound (yield: 76%).

5 ¹H-NMR (CDCl₃, 500MHz) : δ 1.26 (m, 12H), 3.39 (m, 2H), 4.03 (s, 3H), 4.04 (s, 3H), 6.09 (brs, 1H), 6.28 (brs, 1H), 6.42 (d, J=5.5Hz, 1H), 7.08 (d, J=8.5Hz, 2H), 7.26 (m, 1H), 7.29~7.40 (m, 5H), 7.53 (s, 1H), 8.46 (d, J=4.9Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 499 (M⁺)

Example 188

10 N-(2-Chloro-4-nitrophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [224]

15

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (104 mg) was dissolved in toluene (10 ml) with heat, 2-chloro-4-nitrophenyl isocyanate (150 mg) was added, and the admixture was refluxed with heat for 10 minutes. The separated crystals were filtered and then washed with toluene to obtain 172 mg of the title compound (yield: 100%).

20

¹H-NMR (DMSO-d₆, 500MHz) : δ 3.94 (s, 3H), 3.95 (s, 3H), 6.46 (d, J=5.5Hz, 1H), 7.24 (d, J=9.2Hz, 2H), 7.38 (s, 1H), 7.51 (s, 1H), 7.62 (d, J=8.6Hz, 2H), 8.23 (m, 1H), 8.35 (m, 1H), 8.46 (d, J=5.5Hz, 1H), 8.57 (m, 1H), 8.84 (brs, 1H), 9.85 (brs, 1H)

Mass spectrometry data (FD-MS, m/z) : 494 (M⁺), 496 (M⁺+2)

25

Example 189

30 N-(3-Chloro-2-methoxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [225]

35

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (58 mg) was dissolved in toluene (5 ml) with heat, 3-chloro-2-methoxyphenyl isocyanate (0.1 ml) was added, and the admixture was refluxed with heat for 22 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 75 mg of the title compound (yield: 80%).

40

¹H-NMR (CDCl₃, 500MHz) : δ 3.73 (s, 3H), 4.02 (s, 3H), 4.05 (s, 3H), 6.47 (d, J=5.5Hz, 1H), 7.01~7.06 (m, 2H), 7.15 (d, J=8.5Hz, 2H), 7.43 (s, 1H), 7.52 (d, J=9.2Hz, 2H), 7.57 (s, 1H), 7.81 (s, 1H), 8.16~8.19 (m, 2H), 8.50 (d, J=5.5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 479 (M⁺), 481 (M⁺+2)

Example 190

45 N-(2-Chloro-6-methylphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [226]

50

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 2-chloro-6-methylphenyl isocyanate (0.1 ml) was added, and the admixture was refluxed with heat for 17 minutes. The separated crystals were filtered and then washed with toluene to obtain 61 mg of the title compound (yield: 74%).

55

¹H-NMR (DMSO-d₆, 500MHz) : δ 2.28 (s, 3H), 3.94 (s, 3H), 3.94 (s, 3H), 6.43 (d, J=4.9Hz, 1H), 7.18 (d, J=9.2Hz, 2H), 7.20~7.36 (m, 3H), 7.38 (s, 1H), 7.52 (s, 1H), 7.59 (d, J=9.2Hz, 2H), 7.98 (s, 1H), 8.45 (d, J=5.5Hz, 1H), 9.03 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 463 (M⁺), 465 (M⁺+2)

Example 191

5 N-(3-Chloro-6-methoxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [227]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 3-chloro-6-methoxyphenyl isocyanate (111 mg) was added, and the admixture was refluxed with heat for 29 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 84 mg of the title compound (yield: 100%).

15 $^1\text{H-NMR}$ (CDCl₃, 500MHz) : δ 3. 60 (s, 3H), 3. 99 (s, 3H), 4. 05 (s, 3H), 6. 46 (d, J=4. 9Hz, 1H), 6. 69 (d, J=8. 5Hz, 1H), 6. 90 (m, 1H), 7. 11 (d, J=9. 2Hz, 2H), 7. 42 (s, 1H), 7. 53 (d, J=8. 5Hz, 2H), 7. 58 (s, 1H), 7. 82 (s, 1H), 8. 32 (m, 1H), 8. 48 (d, J=5. 5Hz, 1H), 8. 52 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 479 (M⁺), 481 (M⁺+2)

Example 192

20 N-(4-Chloro-3-nitrophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [228]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 4-chloro-3-nitrophenyl isocyanate (224 mg) was added, and the admixture was refluxed with heat for 8 minutes. The separated crystals were filtered and then washed with toluene to obtain 125 mg of the title compound (yield: 75%).

30 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3. 93 (s, 3H), 3. 95 (s, 3H), 6. 46 (d, J=4. 9Hz, 1H), 7. 21 (d, J=8. 5Hz, 2H), 7. 38 (s, 1H), 7. 51 (s, 1H), 7. 60 (d, J=8. 5Hz, 2H), 7. 65 (s, 1H), 7. 67 (s, 1H), 8. 31 (s, 1H), 8. 46 (d, J=4. 9Hz, 1H), 9. 01 (s, 1H), 9. 27 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 463 (M⁺), 465 (M⁺+2)

Example 193

35 N-(2,4-Dichlorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [229]

40 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) was dissolved in toluene (5 ml) with heat, 2,4-dichlorophenyl isocyanate (115 mg) was added, and the admixture was refluxed with heat for 20 minutes. The separated crystals were filtered and then washed with toluene to obtain 74 mg of the title compound (yield: 85%).

45 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 45 (d, J=4. 9Hz, 1H), 7. 22 (d, J=8. 6Hz, 2H), 7. 39 (s, 1H), 7. 40 (m, 1H), 7. 51 (s, 1H), 7. 59 (d, J=9. 2Hz, 2H), 7. 62 (m, 1H), 8. 21 (d, J=9. 2Hz, 1H), 8. 40 (s, 1H), 8. 46 (d, J=5. 5Hz, 1H), 9. 56 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 483 (M⁺)

Example 194

5 N-(2,6-Dichlorophenyl)-N'-(4-[(6,7-dimethoxy-4-
quinolyl)oxy]phenyl)urea [230]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 2,6-dichlorophenyl isocyanate (125 mg) was added, and the admixture was refluxed with heat for 12 minutes. The separated crystals were filtered and then washed with toluene to obtain 81 mg of the title compound (yield: 96%).

15 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 94 (s, 3H), 6. 43 (d, J=5. 5Hz, 1H), 7. 14~7. 20 (m, 2H), 7. 32 (dd, J=7. 9, 7. 9Hz, 1H), 7. 38 (s, 1H), 7. 51~7. 54 (m, 3H), 7. 60 (d, J=9. 2Hz, 2H), 8. 23 (s, 1H), 8. 45 (d, J=5. 5Hz, 1H), 9. 09 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 483 (M⁺)

Example 195

20 N-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)-N'-(1-(1-
naphthyl)ethyl)urea [231]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) was dissolved in toluene (5 ml) with heat, 1-(1-naphthyl)ethyl isocyanate (0.05 ml) was added, and the admixture was refluxed with heat for 100 minutes. The resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 65 mg of the title compound (yield: 72%).

30 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 1. 55 (d, J=6. 7Hz, 3H), 3. 93 (s, 3H), 3. 94 (s, 3H), 4. 62 (m, 1H), 6. 39 (d, J=4. 9Hz, 1H), 6. 79 (s, 1H), 7. 11 (d, J=9. 2Hz, 2H), 7. 36 (s, 1H), 7. 49~7. 58 (m, 7H), 7. 83 (m, 1H), 7. 94 (m, 1H), 8. 17 (m, 1H), 8. 42 (d, J=5. 5Hz, 1H), 8. 52 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 493 (M⁺)

Example 196

35 N-(2-n-Butylphenyl)-N'-(4-[(6,7-dimethoxy-4-
quinolyl)oxy]phenyl)urea [232]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (119 mg) was suspended in toluene (12 ml), after the addition of triethylamine (2.4 ml), triphosgene (133 mg) was added, and the admixture was refluxed with heat for 2 minutes. 2-n-Butylphenylamine (0.13 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 10 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with chloroform, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (4/1) to obtain 130 mg of the title compound (yield: 69%).

50 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 0. 92 (t, J=7. 5Hz, 3H), 1. 32~1. 40 (m, 2H), 1. 50~1. 57 (m, 2H), 2. 59 (t, J=8. 9Hz, 2H), 3. 93 (s, 3H), 3. 94 (s, 3H), 6. 44 (d, J=4. 9Hz, 1H), 6. 98~7. 02 (m, 1H), 7. 12~7. 17 (m, 2H), 7. 19 (d, J=8. 9Hz, 2H), 7. 51 (s, 1H), 7. 58 (s, 1H), 7. 59 (d, J=8. 5Hz, 2H), 7. 71~7. 75 (m, 1H), 7. 89 (s, 1H), 8. 46 (d, J=4. 9Hz, 1H), 9. 11 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 471 (M⁺)

Example 197

5 N-(3-Ethoxycarbonylphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [233]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (131 mg) was dissolved in toluene (10 ml) with heat, after the addition of triethylamine (2 ml), triphosgene (213 mg) was added, and the admixture was refluxed with heat for 2 minutes. Ethyl 15 3-aminobenzoate (0.1 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 7 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 214 mg of the title compound (yield: 100%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 36 (t, J=7. 3Hz, 3H), 4. 02 (s, 3H), 4. 05 (s, 3H), 4. 36 (q, J=7. 3Hz, 2H), 6. 45 (d, J=5. 5Hz, 1H), 7. 13 (d, J=9. 2Hz, 2H), 7. 38~7. 45 (m, 4H), 7. 48 (d, J=9. 2Hz, 2H), 7. 56 (s, 1H), 7. 75 (d, J=7. 3Hz, 1H), 7. 80 (d, J=7. 9Hz, 1H), 7. 90 (s, 1H), 8. 48 (d, J=4. 9Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 487 (M⁺)

20 Example 198

25 N-(2,3-Dichlorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [234]

30 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 2,3-dichlorophenyl isocyanate (0.05 ml) was added, and the admixture was refluxed with heat for 20 minutes. The reaction solution was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 84 mg of the title compound (yield: 100%).

35 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 00 (s, 3H), 4. 05 (s, 3H), 6. 45 (d, J=5. 5Hz, 1H), 7. 11~7. 17 (m, 4H), 7. 41 (s, 1H), 7. 53 (d, J=9. 2Hz, 2H), 7. 57 (s, 1H), 7. 91 (s, 1H), 8. 22 (d, J=8. 5Hz, 1H), 8. 48 (d, J=5. 5Hz, 1H), 9. 12 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 483 (M⁺)

Example 199

40 N-(2,4-Dichlorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [235]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (58 mg) was dissolved in toluene (5 ml) with heat, 2,4-dichlorophenyl isocyanate (93 mg) was added, and the admixture was refluxed with heat for 20 minutes. The reaction solution was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 69 mg of the title compound (yield: 73%).

50 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 04 (s, 3H), 4. 06 (s, 3H), 6. 47 (d, J=4. 9Hz, 1H), 6. 98 (dd, J=2. 4, 8. 5Hz, 1H), 7. 19 (d, J=8. 5Hz, 2H), 7. 25 (s, 1H), 7. 29 (s, 1H), 7. 39 (s, 1H), 7. 43 (s, 1H), 7. 52 (d, J=8. 5Hz, 2H), 7. 56 (s, 1H), 8. 40 (d, J=2. 4Hz, 1H), 8. 50 (d, J=4. 9Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 483 (M⁺)

55

Example 200

5 N-(3,4-Dichlorophenyl)-N'-(4-[(6,7-dimethoxy-4-
quinolyl)oxy]phenyl)urea [236]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, 3,4-dichlorophenyl
 isocyanate (102 mg) was added, and the admixture was refluxed with heat for 8 minutes. The separated crystals were
 filtered and then washed with toluene to obtain 71 mg of the title compound (yield: 84%).

15 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 44 (d, J=4. 9Hz, 1H), 7. 14~7. 24 (m, 2H), 7. 34
 (m, 1H), 7. 38 (s, 1H), 7. 50~7. 52 (m, 2H), 7. 59 (d, J=9. 2Hz, 2H), 7. 88 (s, 1H), 8. 46 (d, J=4. 9Hz, 1H), 8. 92 (s,
 1H), 9. 00 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 483 (M⁺)

Example 201

20 N-(3,5-Dichlorophenyl)-N'-(4-[(6,7-dimethoxy-4-
quinolyl)oxy]phenyl)urea [237]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) was dissolved in toluene (5 ml) with heat, 3,5-dichlorophenyl
 isocyanate (76 mg) was added, and the admixture was refluxed with heat for 8 minutes. The separated crystals were
 filtered and then washed with toluene to obtain 75 mg of the title compound (yield: 87%).

30 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3. 93 (s, 3H), 3. 94 (s, 3H), 6. 44 (d, J=4. 9Hz, 1H), 7. 15 (s, 1H), 7. 20 (d, J=9.
 2Hz, 2H), 7. 38 (s, 1H), 7. 51 (s, 1H), 7. 54 (s, 1H), 7. 54 (s, 1H), 7. 59 (d, J=9. 2Hz, 2H), 8. 46 (d, J=4. 9Hz, 1H),
 9. 00 (brs, 1H), 9. 07 (brs, 1H)
 Mass spectrometry data (FD-MS, m/z) : 483 (M⁺)

Example 202

35 N-(4-Chloro-2-nitrophenyl)-N'-(4-[(6,7-dimethoxy-4-
quinolyl)oxy]phenyl)urea [238]

40 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (123 mg) was dissolved in toluene (12 ml) with heat, 4-chloro-2-nitro-
 phenyl isocyanate (172 mg) was added, and the admixture was refluxed with heat for 14 minutes. The separated crys-
 tals were filtered and then washed with toluene to obtain 174 mg of the title compound (yield: 85%).

45 $^1\text{H-NMR}$ (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 46 (d, J=4. 9Hz, 1H), 7. 23 (d, J=7. 3Hz, 2H), 7. 39
 (s, 1H), 7. 51 (s, 1H), 7. 62 (d, J=7. 3Hz, 2H), 7. 79 (d, J=9. 2Hz, 1H), 8. 14 (s, 1H), 8. 35 (d, J=9. 2Hz, 1H), 8. 46
 (d, J=5. 5Hz, 1H), 9. 62 (s, 1H), 10. 0 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 494 (M⁺), 496 (M⁺+2)

Example 203

5 N-(2-Amino-4-chlorophenyl)-N'-(4-[(6,7-dimethoxy-4-
quinolyl)oxy]phenyl)urea [239]

10 N-(4-Chloro-2-nitrophenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea (158 mg) was dissolved in chloroform/methanol/water (10ml/70ml/5ml), sodium thiosulfate (1.01 g) was added, and the admixture was stirred at 60 °C for 37 minutes. The reaction mixture was extracted 2 times with chloroform, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 33 mg of the title compound (yield: 22%).

15 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 5. 09 (brs, 2H), 6. 43 (d, J=4. 9Hz, 1H), 6. 57 (m, 1H), 6. 78 (d, J=2. 4Hz, 1H), 7. 17 (d, J=9. 2Hz, 2H), 7. 34 (d, J=8. 6Hz, 1H), 7. 38 (s, 1H), 7. 51 (s, 1H), 7. 57 (d, J=8. 5Hz, 2H), 7. 77 (s, 1H), 8. 45 (d, J=4. 9Hz, 1H), 8. 89 (s, 1H)

Example 204

20 N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-pyridinecarbonyl)urea [240]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (75 mg) was dissolved in toluene (7 ml) with heat, after the addition of triethylamine (1.4 ml), triphosgene (201 mg) was added, and the admixture was refluxed with heat for 1 minute. 2-Pyridinecarboxamide (102 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 3 hours. 30 After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 86 mg of the title compound (yield: 77%).

35 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 06 (s, 3H), 4. 06 (s, 3H), 6. 49 (d, J=4. 9Hz, 1H), 7. 20 (d, J=9. 2Hz, 2H), 7. 43 (m, 1H), 7. 57 (s, 1H), 7. 59 (m, 1H), 7. 71 (d, J=9. 2Hz, 2H), 7. 97 (m, 1H), 8. 28 (d, J=7. 9Hz, 1H), 8. 50 (brs, 1H), 8. 68 (d, J=4. 9Hz, 1H), 10. 1 (brs, 1H), 10. 7 (brs, 1H)
 Mass spectrometry data (FD-MS, m/z) : 444 (M⁺)

Example 205

40 N-(3-Chloro-4,6-dimethoxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [241]

45 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) was dissolved in toluene (5 ml) with heat, 3-chloro-4,6-dimethoxyphenyl isocyanate (76 mg) was added, and the admixture was refluxed with heat for 18 minutes. The reaction solution was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 93 mg of the title compound (yield: 100%).

50 ¹H-NMR (CDCl₃, 500MHz) : δ 3. 76 (s, 3H), 3. 87 (s, 3H), 4. 02 (s, 3H), 4. 05 (s, 3H), 6. 46 (d, J=5. 5Hz, 1H), 6. 49 (s, 1H), 7. 13 (d, J=8. 5Hz, 2H), 7. 20 (s, 1H), 7. 42 (s, 1H), 7. 50 (d, J=8. 5Hz, 2H), 7. 57 (s, 1H), 7. 59 (s, 1H), 8. 12 (s, 1H), 8. 48 (d, J=5. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 509 (M⁺), 511 (M⁺+2)

Example 206

5 N-(4-Chloro-2-methylphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [242]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (55 mg) was dissolved in toluene (5 ml) with heat, 4-chloro-2-methylphenyl isocyanate (90 mg) was added, and the admixture was refluxed with heat for 26 minutes. The separated crystals were filtered and then washed with toluene to obtain 69 mg of the title compound (yield: 80%).

15 ¹H-NMR (DMSO-d₆, 500MHz) : δ 2.26 (s, 3H), 3.94 (s, 3H), 3.94 (s, 3H), 6.44 (m, 1H), 7.18~7.20 (m, 3H), 7.25 (s, 1H), 7.38 (s, 1H), 7.51 (s, 1H), 7.59 (d, J=9.2Hz, 2H), 7.87 (m, 1H), 7.99 (s, 1H), 8.45 (m, 1H), 9.15 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 436 (M⁺), 465 (M⁺+2)

Example 207

20 N-(2-Chloro-3-methylphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [243]

25 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 2-chloro-3-methylphenyl isocyanate (0.2 ml) was added, and the admixture was refluxed with heat for 12 minutes. The reaction solution was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 30 mg of the title compound (yield: 37%).

30 ¹H-NMR (CDCl₃, 500MHz) : δ 2.28 (s, 3H), 4.00 (s, 3H), 4.03 (s, 3H), 6.41 (d, J=4.9Hz, 1H), 7.09~7.15 (m, 4H), 7.37 (s, 1H), 7.39 (s, 1H), 7.42 (d, J=8.5Hz, 2H), 7.55 (s, 1H), 7.61 (s, 1H), 7.72 (s, 1H), 8.44 (d, J=5.5Hz, 1H).

Mass spectrometry data (FD-MS, m/z) : 463 (M⁺), 465 (M⁺+2)

Example 208

40 N-(3-Amino-4-chlorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [244]

45 N-(4-Chloro-3-nitrophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea (100 mg) was dissolved in chloroform/methanol/water (5ml/15ml/3ml), sodium thiosulfate (358 mg) was added, and the admixture was stirred at 60 °C for 20 minutes. The reaction mixture was extracted 2 times with chloroform, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 39 mg of the title compound (yield: 41%).

50 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3.94 (s, 3H), 3.95 (s, 3H), 5.30 (brs, 1H), 6.45 (d, J=5.5Hz, 1H), 6.64 (m, 1H), 7.02 (m, 1H), 7.06 (d, J=8.6Hz, 1H), 7.20 (d, J=9.2Hz, 2H), 7.39 (s, 1H), 7.52 (s, 1H), 7.57 (d, J=8.6Hz, 2H), 8.47 (d, J=4.9Hz, 1H), 8.56 (s, 1H), 8.73 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 465 (M⁺+1)

55

Example 209

5 N - (3 - M e t h o x y p r o p y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
quinolyl)oxy]phenyl}urea [245]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (54 mg) was added, and the admixture was refluxed with heat for 2 minutes. 3-Methoxypropylamine (0.05 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 12 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 51 mg of the title compound (yield: 72%).

15 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 82 (m, 2H), 3. 31 (s, 3H), 3. 39 (m, 2H), 3. 50 (t, J=4. 5Hz, 2H), 4. 03 (s, 3H), 4. 04 (s, 3H), 5. 65 (brs, 1H), 6. 44 (d, J=4. 9Hz, 1H), 7. 10 (d, J=8. 7Hz, 2H), 7. 41~7. 55 (m, 4H), 7. 55 (s, 1H), 8. 46 (d, J=5. 5Hz, 1H)
20 Mass spectrometry data (FD-MS, m/z) : 411 (M⁺)

Example 210

25 N - (2 - M e t h o x y e t h y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
quinolyl)oxy]phenyl}urea [246]

30 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (54 mg) was added, and the admixture was refluxed with heat for 3 minutes. 3-Methoxyethylamine (0.05 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 8 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 63 mg of the title compound (yield: 91%).

35 ¹H-NMR (CDCl₃, 500MHz) : δ 3. 36 (s, 3H), 3. 36~3. 53 (m, 4H), 4. 03 (s, 3H), 4. 03 (s, 3H), 5. 81 (brs, 1H), 6. 43 (d, J=5. 5Hz, 1H), 7. 87 (d, J=8. 5Hz, 2H), 7. 40 (s, 1H), 7. 45 (d, J=9. 2Hz, 2H), 7. 55 (s, 1H), 7. 92 (s, 1H), 8. 45 (d, J=4. 9Hz, 1H)
40 Mass spectrometry data (FAB-MS, m/z) : 398 (M⁺⁺¹)

Example 211

45 N - { 4 - [(6 , 7 - D i m e t h o x y - 4 - q u i n o l y l) o x y] p h e n y l } - N ' - (2 -
pyridylmethyl) urea [247]

50 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (54 mg) was added, and the admixture was refluxed with heat for 2 minutes. 2-Pyridylmethylamine (0.05 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 12 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 76 mg of the title compound (yield: 100%).

55 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 00 (s, 3H), 4. 01 (s, 3H), 4. 58 (d, J=5. 5Hz, 2H), 6. 39 (d, J=5. 5Hz, 1H), 6. 66 (m,

1H), 7. 05 (d, J=9. 2Hz, 2H), 7. 18 (m, 1H), 7. 34 (d, J=7. 9Hz, 1H), 7. 39 (s, 1H), 7. 45 (d, J=9. 2Hz, 2H), 7. 54 (s, 1H), 7. 66 (m, 1H), 8. 40 (brs, 1H), 8. 43 (d, J=5. 5Hz, 1H), 8. 47 (d, J=4. 9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 430 (M⁺)

5 Example 212

N-[(4-tert-Butylphenyl)methyl]-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [248]

10

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 2 minutes. (4-tert-Butylphenyl)methylamine (0.05 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 12 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 23 mg of the title compound (yield: 28%).

20

¹H-NMR (CDCl₃, 500MHz) : δ 3. 99 (s, 3H), 4. 01 (s, 3H), 4. 38 (d, J=5. 5Hz, 1H), 5. 81 (brs, 1H), 6. 38 (d, J=4. 9Hz, 1H), 7. 02 (d, J=9. 2Hz, 2H), 7. 20~7. 40 (m, 7H), 7. 52 (s, 1H), 7. 64 (s, 1H), 8. 40 (d, J=5. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 485 (M⁺)

25 Example 213

N-[(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)-N-(3-pyridylmethyl)urea [249]

30

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (56 mg) was added, and the admixture was refluxed with heat for 2 minutes. 3-Pyridylmethylamine (0.05 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 12 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 71 mg of the title compound (yield: 93%).

40

¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 93 (s, 3H), 3. 94 (s, 3H), 4. 34 (d, J=5. 5Hz, 2H), 6. 40 (d, J=4. 9Hz, 1H), 6. 72 (t, J=6. 1Hz, 1H), 7. 12 (d, J=9. 2Hz, 2H), 7. 35 (m, 1H), 7. 37 (s, 1H), 7. 50 (s, 1H), 7. 53 (d, J=9. 2Hz, 2H), 7. 72 (d, J=7. 9Hz, 1H), 8. 43~8. 46 (m, 2H), 8. 53 (s, 1H), 8. 73 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 430 (M⁺)

45

Example 214

N-[(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)-N-(4-pyridylmethyl)urea [250]

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (53 mg) was added, and the admixture was refluxed with heat for 2 minutes. 4-Pyridylmethylamine (0.05 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 12 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed

by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 40 mg of the title compound (yield: 54%).

5 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 01 (s, 3H), 4. 03 (s, 3H), 4. 43 (d, J=5. 5Hz, 2H), 5. 97 (m, 1H), 6. 40 (d, J=5. 5Hz, 1H), 7. 08 (d, J=9. 2Hz, 2H), 7. 20 (d, J=5. 5Hz, 2H), 7. 38 (s, 1H), 7. 42 (d, J=8. 6Hz, 2H), 7. 54 (s, 1H), 7. 81 (s, 1H), 8. 42 (d, J=5. 5Hz, 1H), 8. 49 (d, J=6. 1Hz, 2H)
10 Mass spectrometry data (FD-MS, m/z) : 430 (M⁺)

Example 215

10 N- { 4- [(6 , 7 - Dimethoxy - 4 - quinolyl) oxy] phenyl } - N' - [(4 - dimethylaminophenyl) methyl] urea [251]

15 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 2 minutes. (4-Dimethylaminophenyl)methylamine (104 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 12 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 12 mg of the title compound (yield: 15%).

25 ¹H-NMR (DMSO-d₆, 500MHz) : δ 2. 87 (s, 6H), 3. 93 (s, 3H), 3. 94 (s, 3H), 4. 18 (d, J=5. 5Hz, 2H), 6. 40-6. 43 (m, 2H), 6. 70 (d, J=9. 2Hz, 2H), 7. 13 (d, J=8. 6Hz, 2H), 7. 14 (d, J=8. 6Hz, 2H), 7. 37 (s, 1H), 7. 51 (s, 1H), 7. 52 (d, J=9. 2Hz, 2H), 8. 44 (d, J=4. 9Hz, 1H), 8. 57 (s, 1H)
30 Mass spectrometry data (FD-MS, m/z) : 472 (M⁺)

Example 216

35 N- { 4- [(6 , 7 - Dimethoxy - 4 - quinolyl) oxy] phenyl } - N' - (3 , 5 - dinitrophenyl) urea [252]

40 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (54 mg) was dissolved in toluene (5 ml) with heat, 3,5-dinitrophenyl isocyanate (81 mg) was added, and the admixture was refluxed with heat for 20 minutes. The reaction solution was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 53 mg of the title compound (yield: 57%).

45 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 46 (d, J=4. 9Hz, 1H), 7. 24 (d, J=9. 2Hz, 2H), 7. 39 (s, 1H), 7. 51 (s, 1H), 7. 64 (d, J=8. 5Hz, 2H), 8. 42 (s, 1H), 8. 47 (d, J=4. 9Hz, 1H), 8. 77 (s, 1H), 8. 77 (s, 1H), 9. 21 (s, 1H), 9. 73 (s, 1H)
50 Mass spectrometry data (FD-MS, m/z) : 506 (M⁺+1)

Example 217

55 N - (Cyclohexyl) - N' - { 4 - [(6 , 7 - dimethoxy - 4 - quinolyl) oxy] phenyl } urea [253]

55 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (200 mg) was dissolved in toluene (5 ml) with heat, cyclohexyl isocyanate (340 mg) was added, and the admixture was stirred with heat at 80-90 °C for 30 minutes. After the addition of water, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine

and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 210 mg of the title compound (yield: 74%).

5 ¹H-NMR (CDCl₃, 500MHz) : δ 1. 11~1. 22 (m, 2H), 1. 34~1. 46 (m, 2H), 1. 56~1. 66 (m, 2H), 1. 68~1. 78 (m, 2H),
1. 96~2. 05 (m, 2H), 3. 64~3. 73 (m, 1H), 4. 05 (s, 6H), 4. 58 (d, J=7. 9Hz, 1H), 6. 36 (s, 1H), 6. 46 (d, J=4. 9Hz,
1H), 7. 13 (d, J=8. 6Hz, 2H), 7. 42 (d, J=8. 6Hz, 2H), 7. 42 (s, 1H), 7. 56 (s, 1H), 8. 48 (d, J=4. 9Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 421 (M⁺)

10 Example 218

N-(3, 4-Difluorophenyl)-N'-(4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl)urea [254]

15

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 3,4-Difluoroaniline (66 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 63 mg of the title compound (yield: 83%).

25

¹H-NMR (CDCl₃, 500MHz) : δ 4. 03 (s, 3H), 4. 06 (s, 3H), 6. 45 (d, J=5. 5Hz, 1H), 6. 96~7. 02 (m, 1H), 7. 02~7. 10 (m, 1H), 7. 11 (d, J=8. 5Hz, 2H), 7. 41~7. 45 (m, 2H), 7. 48 (d, J=8. 6Hz, 2H), 7. 58 (s, 1H), 7. 72 (s, 1H), 7. 74 (s, 1H), 8. 44 (d, J=5. 5Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 451 (M⁺)

30

Example 219

N-(2, 4, 5-Trifluorophenyl)-N'-(4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl)urea [255]

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 2,4,5-Trifluoroaniline (75 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 58 mg of the title compound (yield: 73%).

40 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 45 (d, J=5. 5Hz, 1H), 7. 24 (d, J=8. 6Hz, 2H), 7. 40 (s, 1H), 7. 52 (s, 1H), 7. 59 (d, J=8. 6Hz, 2H), 7. 62~7. 70 (m, 1H), 8. 17~8. 25 (m, 1H), 8. 48 (d, J=4. 9Hz, 1H), 8. 76 (s, 1H), 9. 23 (s, 1H)
50 Mass spectrometry data (FD-MS, m/z) : 469 (M⁺)

55

Example 220

5 N-(2,4,6-Trifluorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [256]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 2,4,6-Trifluoroaniline (75 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 37 mg of the title compound (yield: 47%).

15 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3.94 (s, 3H), 3.95 (s, 3H), 6.43 (d, J=5.5Hz, 1H), 7.20 (d, J=8.6Hz, 2H), 7.29 (t, J=8.6Hz, 2H), 7.39 (s, 1H), 7.52 (s, 1H), 7.58 (d, J=8.6Hz, 2H), 8.07 (s, 1H), 8.46 (d, J=5.5Hz, 1H), 9.14 (s, 1H)
20 Mass spectrometry data (FD-MS, m/z) : 469 (M⁺)

Example 221

25 N-(2,3,4-Trifluorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [257]

30 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 2,3,4-Trifluoroaniline (75 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 18 mg of the title compound (yield: 23%).

35 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3.94 (s, 3H), 3.95 (s, 3H), 6.44 (d, J=4.9Hz, 1H), 7.23 (d, J=8.6Hz, 2H), 7.25-7.33 (m, 1H), 7.39 (s, 1H), 7.52 (s, 1H), 7.59 (d, J=8.6Hz, 2H), 7.85-7.92 (m, 1H), 8.47 (d, J=5.5Hz, 1H), 8.73 (s, 1H), 9.21 (s, 1H)
40 Mass spectrometry data (FD-MS, m/z) : 469 (M⁺)

Example 222

45 N-(2,5-Dimethoxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [258]

50 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (56 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (66 mg) was added, and the admixture was refluxed with heat for 3 minutes. 2,5-Dimethoxyaniline (102 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 10 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 81 mg of the title compound (yield: 90%).

¹H-NMR (CDCl₃, 500MHz) : δ 3. 68 (s, 3H), 3. 78 (s, 3H), 4. 02 (s, 3H), 4. 05 (s, 3H), 6. 46 (d, J=5. 5Hz, 1H), 6. 53 (dd, J=3. 1, 8. 5Hz, 1H), 6. 76 (d, J=9. 2Hz, 1H), 7. 13 (d, J=9. 2Hz, 2H), 7. 43 (s, 1H), 7. 52 (d, J=9. 2Hz, 2H), 7. 55 (s, 1H), 7. 57 (s, 1H), 7. 78 (s, 1H), 7. 91 (d, J=3. 1Hz, 1H), 8. 49 (d, J=4. 9Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 475 (M⁺)

5

Example 223

N-(3,5-Dimethoxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [259]

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (101 mg) was added, and the admixture was refluxed with heat for 4 minutes. 3,5-Dimethoxyaniline (62 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 13 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 85 mg of the title compound (yield: 100%).

¹H-NMR (CDCl₃, 500MHz) : δ 3. 73 (s, 6H), 4. 00 (s, 3H), 4. 03 (s, 3H), 6. 18 (s, 1H), 6. 42 (d, J=5. 5Hz, 1H), 6. 60 (s, 1H), 6. 60 (s, 1H), 7. 09 (d, J=8. 6Hz, 2H), 7. 40 (s, 1H), 7. 45 (d, J=8. 6Hz, 2H), 7. 56 (s, 1H), 7. 68 (s, 1H), 7. 85 (s, 1H), 8. 45 (d, J=5. 5Hz, 1H)
 Mass spectrometry data (FD-MS, m/z) : 475 (M⁺)

25

Example 224

N-(2,3-Difluorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [260]

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 2,3-Difluoroaniline (51 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 60 mg of the title compound (yield: 79%).

¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 45 (d, J=4. 9Hz, 1H), 7. 02~7. 08 (m, 1H), 7. 11~7. 19 (m, 1H), 7. 23 (d, J=9. 2Hz, 2H), 7. 39 (s, 1H), 7. 52 (s, 1H), 7. 59 (d, J=9. 2Hz, 2H), 7. 94~7. 99 (m, 1H), 8. 47 (d, J=4. 9Hz, 1H), 8. 78 (s, 1H), 9. 25 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 451 (M⁺)

45

Example 225

N-(3,5-Difluorophenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [261]

55

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 3,5-Difluoroaniline (66 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes.

After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 49 mg of the title compound (yield: 64%).

5

¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 45 (d, J=4. 9Hz, 1H), 6. 75~6. 83 (m, 1H), 7. 16~7. 26 (m, 4H), 7. 39 (s, 1H), 7. 52 (s, 1H), 7. 59 (d, J=8. 6Hz, 2H), 8. 47 (d, J=4. 9Hz, 1H), 8. 99 (s, 1H), 9. 12 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 451 (M⁺)

10 Example 226

N-(2, 3, 6-Trifluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}urea [262]

15

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 2,3,6-trifluoroaniline (53 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 30 mg of the title compound (yield: 38%).

25

¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 93 (s, 3H), 3. 94 (s, 3H), 6. 44 (d, J=5. 5Hz, 1H), 7. 15~7. 25 (m, 3H), 7. 33~7. 44 (m, 2H), 7. 52 (s, 1H), 7. 59 (d, J=8. 6Hz, 2H), 8. 41 (s, 1H), 8. 46 (d, J=4. 9Hz, 1H), 9. 18 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 469 (M⁺)

30 Example 227

N-(2, 6-Difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}urea [263]

35

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, 2,6-difluorophenyl isocyanate (104 mg) was added, and the admixture was refluxed with heat for 30 minutes. The separated crystals were filtered and then washed with toluene to obtain 57 mg of the title compound (yield: 74%).

¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 44 (d, J=4. 9Hz, 1H), 7. 13~7. 25 (m, 4H), 7. 28~7. 38 (m, 1H), 7. 39 (s, 1H), 7. 52 (s, 1H), 7. 59 (d, J=9. 2Hz, 2H), 8. 15 (s, 1H), 8. 46 (d, J=5. 5Hz, 1H), 9. 09 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 451 (M⁺)

45

Example 228

N-(2, 5-Bis(trifluoromethyl)phenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}urea [264]

55

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 2,5-Bis(trifluoromethyl)aniline (79 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent

was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 30 mg of the title compound (yield: 32%).

5 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 45 (d, J=4. 9Hz, 1H), 7. 24 (d, J=9. 2Hz, 2H), 7. 40 (s, 1H), 7. 52 (s, 1H), 7. 60~7. 66 (m, 3H), 7. 95 (d, J=7. 9Hz, 1H), 8. 38 (s, 1H), 8. 46~8. 52 (m, 2H), 9. 70 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 551 (M⁺)

Example 229

10 N - (2 , 4 - D i m e t h o x y p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
q u i n o l y l) o x y] p h e n y l } u r e a [2 6 5]

15 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (51 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (72 mg) was added, and the admixture was refluxed with heat for 3 minutes. 2,4-Dimethoxyaniline (60 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 11 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, 20 and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 44 mg of the title compound (yield: 53%).

25 ¹H-NMR (CDCl₃, 500MHz) : δ 3. 74 (s, 3H), 3. 80 (s, 3H), 4. 03 (s, 3H), 4. 05 (s, 3H), 6. 44~6. 51 (m, 3H), 7. 06 (s, 1H), 7. 12 (d, J=9. 2Hz, 2H), 7. 43 (s, 1H), 7. 49~7. 51 (m, 3H), 7. 57 (s, 1H), 7. 86 (d, J=8. 6Hz, 1H), 8. 48 (d, J=5. 5Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 475 (M⁺)

Example 230

30 N - (2 - C h l o r o p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
q u i n o l y l) o x y] p h e n y l } u r e a [2 6 6]

35 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 2-chlorophenyl isocyanate (0.05 ml) was added, and the admixture was refluxed with heat for 30 minutes. The reaction solution was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 64 mg of the title 40 compound (yield: 81%).

45 ¹H-NMR (CDCl₃, 500MHz) : δ 4. 01 (s, 3H), 4. 05 (s, 3H), 6. 46 (d, J=4. 9Hz, 1H), 6. 98 (dd, J=7. 3, 7. 9Hz, 1H), 7. 14 (d, J=8. 6Hz, 2H), 7. 26 (dd, J=7. 3, 7. 9Hz, 1H), 7. 31 (d, J=7. 9Hz, 1H), 7. 43 (s, 1H), 7. 52 (d, J=9. 2Hz, 2H), 7. 57 (s, 1H), 7. 57 (s, 1H), 8. 24 (d, J=7. 9Hz, 1H), 8. 37 (s, 1H), 8. 50 (d, J=5. 5Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 449 (M⁺), 451 (M⁺+2)

Example 231

50 N - (3 - C h l o r o p h e n y l) - N ' - { 4 - [(6 , 7 - d i m e t h o x y - 4 -
q u i n o l y l) o x y] p h e n y l } u r e a [2 6 7]

55 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, 2-chlorophenyl isocyanate (0.05 ml) was added, and the admixture was refluxed with heat for 30 minutes. The reaction solution was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 72 mg of the title compound (yield: 93%).

¹H-NMR (CDCl₃, 500MHz) : δ 3. 98 (s, 3H), 4. 03 (s, 3H), 6. 41 (d, J=4. 9Hz, 1H), 6. 99 (d, J=7. 9Hz, 1H), 7. 09 (d, J=8. 5Hz, 2H), 7. 16 (dd, J=7. 9Hz, 7. 9Hz, 1H), 7. 23 (d, J=8. 6Hz, 1H), 7. 38 (s, 1H), 7. 42~7. 44 (m, 3H), 7. 56 (s, 1H), 8. 13 (s, 1H), 8. 14 (s, 1H), 8. 44 (d, J=5. 5Hz, 1H)

Mass spectrometry data (FD-MS, m/z) : 449 (M⁺), 451 (M⁺+2)

5

Example 232

10

N-(2,3-Dimethoxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [268]

15 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (74 mg) was added, and the admixture was refluxed with heat for 3 minutes. 2,3-Dimethoxyaniline (0.05 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 11 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 83 mg of the title compound (yield: 100%).

20

¹H-NMR (CDCl₃, 500MHz) : δ 3. 72 (s, 3H), 3. 84 (s, 3H), 4. 02 (s, 3H), 4. 05 (s, 3H), 6. 46 (d, J=5. 5Hz, 1H), 6. 62 (d, J=7. 9Hz, 1H), 7. 05 (dd, J=8. 5, 8. 5Hz, 1H), 7. 13 (d, J=9. 2Hz, 2H), 7. 43 (s, 1H), 7. 54 (d, J=8. 6Hz, 2H), 7. 58 (s, 1H), 7. 85 (d, J=8. 6Hz, 1H), 7. 88 (s, 1H), 8. 27 (s, 1H), 8. 50 (d, J=5. 5Hz, 1H)

25

Mass spectrometry data (FD-MS, m/z) : 475 (M⁺)

Example 233

30

N-(4-Hydroxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [269]

35

N-(4-Benzylxyphenyl)-N'-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}urea (228 mg) was dissolved in N,N-dimethylformamide/ethyl acetate (15 ml/20 ml), after the addition of triethylamine (4 ml), 20% palladium hydroxide (1.18 g) was added, and the admixture was stirred at room temperature under hydrogen for 15 hours. The reaction mixture was filtered using Celite, after which the filtrate was concentrated, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 188 mg of the title compound (yield: 100%).

40

¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 98 (s, 3H), 3. 99 (s, 3H), 6. 60 (d, J=5. 5Hz, 1H), 6. 68 (d, J=8. 6Hz, 2H), 7. 21 (d, J=8. 5Hz, 2H), 7. 22 (d, J=8. 5Hz, 2H), 7. 47 (s, 1H), 7. 60 (d, J=9. 2Hz, 2H), 7. 61 (s, 1H), 8. 58 (s, 1H), 8. 59 (s, 1H), 8. 98 (s, 1H), 9. 03 (s, 1H)

Mass spectrometry data (FD-MS, m/z) : 431 (M⁺+1)

45

Example 234

50

N-(4-Acetoxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [270]

55

N-(4-Hydroxyphenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea (47 mg) was dissolved in methylene chloride (6 ml), after the addition of triethylamine (2 ml), acetic anhydride (0.5 ml) was added, and the admixture was stirred at room temperature for 15 hours. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column

chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 35 mg of the title compound (yield: 68%).

5 $^1\text{H-NMR}$ (CDCl_3 , 500MHz) : δ 2. 31 (s, 3H), 4. 01 (s, 3H), 4. 04 (s, 3H), 6. 43 (d, $J=5. 5\text{Hz}$, 1H), 7. 01 (d, $J=8. 6\text{Hz}$, 2H), 7. 11 (d, $J=9. 2\text{Hz}$, 2H), 7. 26 (brs, 1H), 7. 32 (d, $J=9. 2\text{Hz}$, 2H), 7. 40 (s, 1H), 7. 45 (d, $J=9. 2\text{Hz}$, 1H), 7. 56 (s, 1H), 7. 56 (brs, 1H), 8. 46 (d, $J=4. 9\text{Hz}$, 1H)
 Mass spectrometry data (FD-MS, m/z) : 473 (M^+)

Example 235

10 $\text{N}-(3, 4, 5\text{-Trimethoxyphenyl})-\text{N}'-\{4-[(6, 7\text{-dimethoxy-4-quinolyl)oxy]phenyl}\}urea$ [271]

15

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (66 mg) was added, and the admixture was refluxed with heat for 2 minutes. 3,4,5-Trimethoxyaniline (76 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 19 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, 20 and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 76 mg of the title compound (yield: 87%).

25 $^1\text{H-NMR}$ (CDCl_3 , 500MHz) : δ 3. 81 (s, 6H), 3. 83 (s, 3H), 4. 02 (s, 3H), 4. 05 (s, 3H), 6. 44 (d, $J=4. 9\text{Hz}$, 1H), 6. 69 (s, 2H), 7. 12 (d, $J=9. 2\text{Hz}$, 2H), 7. 41 (s, 1H), 7. 41 (brs, 1H), 7. 48 (d, $J=8. 6\text{Hz}$, 2H), 7. 57 (s, 1H), 7. 58 (s, 1H), 8. 47 (d, $J=4. 9\text{Hz}$, 1H)
 Mass spectrometry data (FD-MS, m/z) : 505 (M^+)

Example 236

30 $\text{N}-(2, 4\text{-Difluorophenyl})-\text{N}'-\{4-[(6, 7\text{-dimethoxy-4-quinolyl)oxy]phenyl}\}urea$ [272]

35

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (100 mg) was dissolved in toluene (10 ml) with heat, 2,4-difluorophenyl isocyanate (120 ml) was added, and the admixture was refluxed with heat for 30 minutes. The separated crystals were filtered and then washed with toluene to obtain 128 mg of the title compound (yield: 84%).

40

$^1\text{H-NMR}$ (DMSO-d_6 , 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 46 (d, $J=4. 9\text{Hz}$, 1H), 7. 03~7. 10 (m, 1H), 7. 22 (d, $J=9. 2\text{Hz}$, 2H), 7. 28~7. 35 (m, 1H), 7. 39 (s, 1H), 7. 52 (s, 1H), 7. 59 (d, $J=9. 2\text{Hz}$, 2H), 8. 05~8. 12 (m, 1H), 8. 47 (d, $J=5. 5\text{Hz}$, 1H), 8. 52 (s, 1H), 9. 15 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 451 (M^+)

45

Example 237

50 $\text{N}-(2, 5\text{-Difluorophenyl})-\text{N}'-\{4-[(6, 7\text{-dimethoxy-4-quinolyl)oxy]phenyl}\}urea$ [273]

55

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (100 mg) was dissolved in toluene (10 ml) with heat, 2,5-difluorophenyl isocyanate (120 ml) was added, and the admixture was refluxed with heat for 30 minutes. The separated crystals were filtered and then washed with toluene to obtain 132 mg of the title compound (yield: 87%).

$^1\text{H-NMR}$ (DMSO-d_6 , 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 46 (d, $J=5. 5\text{Hz}$, 1H), 6. 80~6. 87 (m, 1H), 7. 23

(d, J=9. 2Hz, 2H), 7. 27~ 7. 33 (m, 1H), 7. 40 (s, 1H), 7. 52 (s, 1H), 7. 59 (d, J=8. 6Hz, 2H), 8. 03~8. 08 (m, 1H), 8. 47 (d, J=5. 5Hz, 1H), 8. 78 (s, 1H), 9. 27 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 451 (M⁺)

5 Example 238

N-(4-Amino-2-chlorophenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea [274]

10

N-(4-Chloro-3-nitrophenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea (150 mg) was dissolved in chloroform/methanol/water (10 ml/13 ml/3 ml), sodium thiosulfate (501 mg) was added, and the admixture was stirred at 60 °C for 50 minutes. The reaction mixture was extracted 2 times with chloroform, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 48 mg of the title compound (yield: 34%).

20 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 94 (s, 3H), 5. 14 (brs, 2H), 6. 43 (d, J=4. 9Hz, 1H), 6. 51 (m, 1H), 6. 65 (d, J=2. 5Hz, 1H), 7. 17 (d, J=9. 2Hz, 2H), 7. 38 (s, 1H), 7. 48 (d, J=8. 6Hz, 1H), 7. 51 (s, 1H), 7. 56 (d, J=8. 5Hz, 2H), 7. 83 (s, 1H), 8. 45 (d, J=5. 5Hz, 1H), 9. 10 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 464 (M⁺), 466 (M⁺⁺²)

25 Example 239

N-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}-N'-[2-ethoxycarbonylphenyl] urea [275]

30

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (100 mg) was dissolved in toluene (10 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (100 mg) was added, and the admixture was refluxed with heat for 2 minutes. Ethyl 2-aminobenzoate (84 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 2 hours. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 86 mg of the title compound (yield: 52%).

40

¹H-NMR (DMSO-d₆, 90MHz) : δ 1. 37 (t, J=7Hz, 3H), 3. 94 (s, 3H), 3. 94 (s, 3H), 4. 38 (q, J=7Hz, 2H), 6. 47 (d, J=5Hz, 1H), 7. 1~8. 1 (m, 9H), 8. 38 (d, J=9Hz, 1H), 8. 47 (d, J=5Hz, 1H), 9. 92 (s, 1H), 10. 10 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 487 (M⁺)

45 Example 240

N-(2-Methylthiophenyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea [276]

50

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (131 mg) was dissolved in toluene (13 ml) with heat, after the addition of triethylamine (2.6 ml), triphosgene (152 mg) was added, and the admixture was refluxed with heat for 2 minutes. 2-Methylthioaniline (0.11 ml) was added to the reaction mixture, and the admixture was refluxed with heat for 10 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with chloroform, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting

with chloroform/acetone (4/1) to obtain 29 mg of the title compound (yield: 14%).

5 ¹H-NMR (DMSO-d₆, 500MHz) : δ 2. 50 (s, 3H), 4. 00 (s, 3H), 4. 00 (s, 3H), 6. 51 (d, J=5. 5Hz, 1H), 7. 08~7. 15 (m, 1H), 7. 25~7. 35 (m, 3H), 7. 45 (s, 1H), 7. 48 (d, J=7. 9Hz, 1H), 7. 58 (s, 1H), 7. 67 (d, J=8. 5Hz, 2H), 7. 99 (d, J=7. 9Hz, 1H), 8. 24 (s, 1H), 8. 53 (d, J=5. 5Hz, 1H), 9. 61 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 461 (M⁺)

Example 241

10 N-[3, 5-Bis(trifluoromethyl)phenyl]-N'-(4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl)urea [277]

15 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 3,5-Bis(trifluoromethyl)aniline (116 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with 20 ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 54 mg of the title compound (yield: 58%).

25 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 93 (s, 3H), 3. 94 (s, 3H), 6. 45 (d, J=5. 5Hz, 1H), 7. 23 (d, J=9. 2Hz, 2H), 7. 39 (s, 1H), 7. 51 (d, J=9. 2Hz, 2H), 7. 62 (d, J=9. 2Hz, 2H), 7. 64 (s, 1H), 8. 15 (s, J=5. 5Hz, 2H), 9. 13 (s, 1H), 9. 43 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 551 (M⁺)

Example 242

30 N-(3-Chloropropyl)-N'-(4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl)urea [278]

35 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (50 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 3-Chloropropylaniline (66 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 20 minutes. 40 After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 26 mg of the title compound (yield: 37%).

45 ¹H-NMR (DMSO-d₆, 500MHz) : δ 1. 87~1. 94 (m, 2H), 3. 20~3. 27 (m, 2H), 3. 69 (t, J=6. 1Hz, 2H), 3. 93 (s, 3H), 3. 94 (s, 3H), 6. 29 (t, J=6. 1Hz, 1H), 6. 41 (d, J=5. 5Hz, 1H), 7. 14 (d, J=9. 2Hz, 2H), 7. 38 (s, 1H), 7. 50~7. 55 (m, 3H), 8. 46 (d, J=4. 9Hz, 1H), 8. 61 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 415 (M⁺)

50 Example 243

N-[5-[2-(4-fluoro)phenoxy]-pyridyl]-N'-(4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl)urea [279]

55

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (53 mg) was dissolved in toluene (5 ml) with heat, after the addition

of triethylamine (1 ml), triphosgene (58 mg) was added, and the admixture was refluxed with heat for 4 minutes. 5-Amino-2-(4-fluoro)phenoxyqupyridine (95 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 19 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 74 mg of the title compound (yield: 79%).

¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 44 (d, J=5. 5Hz, 1H), 7. 01 (d, J=8. 5Hz, 1H), 7. 12~7. 24 (m, 6H), 7. 38 (s, 1H), 7. 51 (s, 1H), 7. 59 (d, J=9. 2Hz, 2H), 8. 01 (d, J=8. 6Hz, 1H), 8. 19 (d, J=2. 4Hz, 1H), 8. 46 (d, J=4. 9Hz, 1H), 8. 77 (s, 1H), 8. 89 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 526 (M⁺)

Example 244

¹⁵ N - { 4 - [(6 , 7 - Dimethoxy - 4 - quinolyl) oxy] phenyl } - N ' - (3 - dimethylaminophenyl) urea [280]

²⁰ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (52 mg) was dissolved in toluene (5 ml) with heat, after the addition of triethylamine (1 ml), triphosgene (55 mg) was added, and the admixture was refluxed with heat for 3 minutes. 3-Dimethylaminoaniline (69 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 12 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted 2 times with ethyl acetate, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was purified by column chromatography on silica gel eluting with chloroform/acetone (10/1) to obtain 72 mg of the title compound (yield: 89%).

³⁰ ¹H-NMR (CDCl₃, 500MHz) : δ 2. 92 (s, 6H), 4. 01 (s, 3H), 4. 03 (s, 3H), 6. 41 (d, J=4. 9Hz, 1H), 6. 48 (d, J=8. 6Hz, 1H), 6. 56 (d, J=9. 2Hz, 1H), 6. 88 (s, 1H), 7. 08 (d, J=9. 2Hz, 2H), 7. 14 (dd, J=7. 9, 8. 5Hz, 1H), 7. 35 (s, 1H), 7. 41 (s, 1H), 7. 45 (d, J=9. 2Hz, 2H), 7. 55 (s, 1H), 7. 67 (s, 1H), 8. 45 (d, J=4. 9Hz, 1H)
Mass spectrometry data (FD-MS, m/z) : 458 (M⁺)

Example 245

³⁵ N - (2 - Hydroxyphenyl) - N ' - { 4 - [(6 , 7 - dimethoxy - 4 - quinolyl) oxy] phenyl } urea [281]

⁴⁰ 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (105 mg) was dissolved in toluene (10 ml) with heat, after the addition of triethylamine (2 ml), triphosgene (118 mg) was added, and the admixture was refluxed with heat for 2 minutes. 2-Aminophenol (77 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 10 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted with chloroform, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was washed with chloroform and filtered to obtain 86 mg of the title compound (yield: 56%).

⁵⁰ ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 45 (d, J=4. 9Hz, 1H), 6. 73~6. 88 (m, 3H), 7. 20 (d, J=8. 6Hz, 2H), 7. 39 (s, 1H), 7. 52 (s, 1H), 7. 59 (d, J=8. 6Hz, 2H), 8. 03~8. 08 (m, 1H), 8. 19 (s, 1H), 8. 47 (d, J=5. 5Hz, 1H), 9. 46 (s, 1H), 9. 95 (s, 1H)
Mass spectrometry data (FD-MS, m/z) : 431 (M⁺)

Example 246

5 N-(3-Hydroxyphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [282]

10 6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (115 mg) was dissolved in toluene (12 ml) with heat, after the addition of triethylamine (2 ml), triphosgene (113 mg) was added, and the admixture was refluxed with heat for 2 minutes. 3-Aminophenol (73 mg) was added to the reaction mixture, and the admixture was refluxed with heat for 10 minutes. After the addition of aqueous sodium hydrogen carbonate, the reaction mixture was extracted with chloroform, and the organic layer was then washed with brine and dried with anhydrous sodium sulfate. The solvent was removed by reduced-pressure distillation, and the resulting residue was washed with chloroform and filtered to obtain 95 mg of the title compound (yield: 60%).

15 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 35~6. 42 (m, 1H), 6. 44 (d, J=4. 9Hz, 1H), 6. 77~6. 85 (m, 1H), 6. 98~7. 08 (m, 2H), 7. 20 (d, J=8. 6Hz, 2H), 7. 39 (s, 1H), 7. 52 (s, 1H), 7. 58 (d, J=8. 6Hz, 2H), 8. 47 (d, J=4. 9Hz, 1H), 8. 57 (s, 1H), 8. 73 (s, 1H), 9. 31 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 431 (M⁺)

20 Example 247

25 N-(3-Hydroxycarbonylphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea [283]

30 N-(3-Ethoxycarbonylphenyl)-N'-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea (190 mg) obtained in Example 197 was dissolved in methanol (3 ml), 35% aqueous potassium hydroxide (5 ml) was added, and the admixture was stirred at room temperature for 30 minutes. After removing methanol by reduced-pressure distillation and neutralizing using dilute hydrochloric acid, the separated crystals were filtered to obtain 67 mg of the title compound (yield: 38%).

35 ¹H-NMR (DMSO-d₆, 500MHz) : δ 3. 94 (s, 3H), 3. 95 (s, 3H), 6. 45 (d, J=5. 5Hz, 1H), 7. 20 (d, J=8. 6Hz, 2H), 7. 38~7. 65 (m, 7H), 8. 13 (s, 1H), 8. 46 (d, J=4. 9Hz, 1H), 8. 88 (s, 1H), 8. 97 (s, 1H)
 Mass spectrometry data (FD-MS, m/z) : 459 (M⁺)

Test Example 1

40 As for pharmacological action of the compounds of the present invention, inhibition of PDGF receptor autophosphorylation was studied using cultured rat mesangial cells which are known to have the PDGF receptor.

1. Cultivation of rat mesangial cells

45 Kidneys were taken out from Wistar-Kyoto rats (purchased from Charles River Japan, Inc.), and the glomeruli were isolated by the sieving method (Nephron, 22, 454 (1978)). The glomeruli were cultured in RPMI 1640 medium (hereinafter referred to as the medium) containing 10% fetal calf serum (hereinafter abbreviated to FCS) at 37 °C in an incubator in an atmosphere containing 5% carbon dioxide. The glomerulus-derived adhesive cells were subcultured several times to obtain mesangial cells. The mesangial cells subcultured more than 5 passages were used for the assay.

50 2. Evaluation of PDGF receptor autophosphorylation inhibition

55 The mesangial cells were seeded in 24-well flat-bottom microtiter plates and then cultured in the medium containing 10% FCS for 2 days. When the cells were grown to about 3 x 10⁴ cells per well, the medium was changed to the medium containing 0.5% FCS, the cultivation was continued for another 3 days, and then cell growth was arrested. The culture medium was removed, the adhered cells were washed with 500 µl of the medium, and 250 µl of the medium containing 0.1% bovine serum albumin (hereinafter abbreviated to BSA) was then added. A test drug dissolved in 1.38 µl of dimethyl sulfoxide (hereinafter abbreviated to DMSO) was added to this culture medium, and the admixture was

incubated at 37 °C for 1 hour. Recombinant human platelet-derived growth factor BB chain (hereinafter abbreviated to PDGF-BB) was dissolved in the medium containing 0.1% BSA, 25 µl per well of the solution was added at final 50 ng/ml, and the incubation was continued at 37 °C for 10 minutes. The medium was removed, the cells were washed with 500 µl of phosphate-buffered physiological saline (pH 7.4) (hereinafter abbreviated to PBS), and 50 µl of lysis buffer (Tris-buffered physiological saline, pH 7.4, containing 1% Triton X100, 2 mM sodium orthovanadate, and 1 mM ethylene-diamine-tetraacetic acid disodium (hereinafter abbreviated to EDTA) were added. The cells were allowed to stand at 4 °C for 30 minutes for lysis, and the resulting solution was thoroughly admixed with an equal amount of Tris-buffered physiological saline containing 1% sodium dodecyl sulfate (hereinafter abbreviated to SDS). An aliquot (20 µl) of the solution was subjected to SDS electrophoresis on 7.5% polyacrylamide gel. After the electrophoresis, proteins in the gel were electrically transferred to a PVDF filter, which was then subjected to Western blotting using monoclonal antibodies against phosphotyrosine. Bands of PDGF receptor (molecular weight: about 180 KDa) which were autophosphorylated due to the addition of PDGF-BB were quantitated by a densitometer. Autophosphorylation rates for individual wells with drugs were calculated by setting measurements for PDGF receptor autophosphorylation in the wells without drugs in the presence and absence of PDGF-BB as 100% and 0%, respectively.

PDGF receptor autophosphorylation inhibition rates were obtained at a series of different concentrations of individual test drugs, from which regression line formulas were determined to calculate PDGF receptor autophosphorylation 50% inhibition concentrations (IC₅₀s) for the test drugs.

The compounds of the present invention showed the PDGF receptor autophosphorylation 50% inhibition concentrations (IC₅₀s) of less than 100 µM.

As for representative examples of preferred compound groups of the present invention, test results for PDGF receptor autophosphorylation 50% inhibition concentrations (IC₅₀s) in mesangial cells are shown in Table 2.

25

30

35

40

45

50

55

TABLE 2

5

Compound No.	IC ₅₀ (μM) for PDGF receptor autophosphorylation inhibition
10 (2)	0. 44
15 (6)	0. 45
15 (8)	0. 10
15 (16)	0. 05
20 (29)	0. 80
20 (32)	0. 30
25 (43)	0. 005
25 (44)	0. 006
25 (45)	0. 014
25 (46)	0. 021
30 (47)	0. 043
30 (49)	0. 018
35 (50)	0. 067
35 (51)	0. 009
35 (52)	0. 03
40 (53)	0. 010
40 (54)	0. 003
40 (55)	0. 003
45 (56)	0. 004
45 (57)	0. 006
45 (58)	0. 002
50 (59)	0. 004
50 (60)	0. 004
50 (63)	0. 40
55 (66)	0. 13
55 (67)	0. 11
55 (68)	0. 44

55

	(6 9)	0. 0 5
5	(7 4)	0. 3 4
	(7 5)	0. 1 8
	(7 9)	0. 3 4
	(9 4)	0. 0 2 3
10	(1 1 3)	0. 0 0 4
	(1 1 4)	0. 0 0 4
	(1 3 1)	0. 0 0 3
15	(1 3 3)	0. 0 0 7
	(1 3 5)	0. 0 4 3
	(1 3 8)	0. 0 1 4
20	(1 3 9)	0. 0 0 5
	(1 6 3)	0. 0 0 5
	(1 6 5)	0. 0 1 0
25	(1 6 6)	0. 0 1 1
	(1 6 7)	0. 0 0 4
	(1 6 8)	0. 0 0 6
30	(1 6 9)	0. 0 0 4
	(1 7 0)	0. 0 1 8
	(1 7 2)	0. 0 1 0
35	(1 7 3)	0. 0 1 6
	(1 7 4)	0. 0 0 2
	(1 7 5)	0. 0 0 6
40	(1 8 8)	0. 0 0 6
	(1 8 9)	0. 0 1 1
	(1 9 0)	0. 0 2 1
45	(1 9 2)	0. 0 0 4
	(1 9 4)	0. 0 1 4
	(1 9 5)	0. 0 7 9
50	(1 9 6)	0. 0 3 1
	(1 9 7)	0. 0 1 0
	(1 9 8)	0. 0 1 1

	(1 9 9)	0. 0 0 3
5	(2 0 0)	0. 0 0 4
	(2 2 0)	0. 0 0 9
	(2 2 4)	0. 0 8 7
10	(2 2 5)	0. 0 4 7
	(2 2 6)	0. 0 1 1
	(2 2 7)	0. 0 7 3
	(2 2 8)	0. 0 5 5
15	(2 2 9)	0. 0 3 7
	(2 3 0)	0. 0 3 4
	(2 3 1)	0. 0 1 9
20	(2 3 2)	0. 0 1 8
	(2 3 3)	0. 0 1 3
	(2 3 4)	0. 0 2 4
25	(2 3 5)	0. 0 4 3
	(2 3 6)	0. 0 5 5
	(2 3 7)	0. 0 7 5
30	(2 3 8)	0. 0 1 6
	(2 3 9)	0. 0 0 5
	(2 4 0)	0. 1 5
35	(2 4 1)	0. 0 1 8
	(2 4 2)	0. 0 1 8
	(2 4 3)	0. 0 1 4
40	(2 4 4)	0. 0 0 9
	(2 4 5)	0. 0 0 6
	(2 4 6)	0. 0 1 3
45	(2 4 7)	0. 0 0 9
	(2 4 8)	0. 0 6 3
	(2 4 9)	0. 0 4 1
50	(2 5 0)	0. 0 1 7
	(2 5 1)	0. 0 3 6
	(2 5 3)	0. 0 0 7

	(254)	0. 007
5	(255)	0. 015
	(256)	0. 004
	(257)	0. 007
10	(258)	0. 007
	(259)	0. 005
	(260)	0. 002
15	(261)	0. 010
	(262)	0. 002
	(263)	0. 004
20	(265)	0. 005
	(266)	0. 001
	(267)	0. 15
25	(268)	0. 007
	(269)	0. 008
	(270)	0. 006
30	(271)	0. 004
	(272)	0. 003
	(273)	0. 005
35	(274)	0. 036
	(276)	0. 005
	(278)	0. 003
40	(279)	0. 029
	(281)	0. 012
45	(282)	0. 008
	(283)	0. 002
	(288)	0. 024
50	(289)	0. 032
	(290)	<u>0. 055</u>

Test Example 2Effect on nephritis associated with mesangial cell growth in rats

5 Groups of 6 Wistar-Kyoto male rats (7 weeks old, purchased from Charles River Japan, Inc.) were used. OX-7 (prepared according to Pathol. Int., 45, 409 (1995)), a monoclonal antibody against anti-rat Thy.1, was injected intravenously into the tails of rats at a dose of 1.2 mg/kg to induce glomerulonephritis associated with mesangial cell growth and extracellular matrix accumulation. A test drug suspended in a vehicle, a 1% aqueous cremophor solution, was administered orally 2 times a day starting one day after an OX-7 injection for 8 consecutive days. On day 9, when pathological changes in glomeruli became markedly apparent, the rats were sacrificed and anatomized under anesthesia with ether, and left kidneys were taken out and fixed in formalin. The kidneys were embedded in paraffin and then sectioned thinly, and the sections were stained with a periodic acid-Schiff's reagent. The 20 glomeruli were arbitrarily selected for individual specimens thus prepared, and pathological sclerotic changes were scored as follows:

15 0: No pathological sclerotic changes were observed in glomeruli.
 1: Pathological sclerotic changes were observed in less than 25% of glomeruli.
 2: Pathological sclerotic changes were observed in 25-50% of glomeruli.
 3: Pathological sclerotic changes were observed in 50-75% of glomeruli.
 4: Pathological sclerotic changes were observed in 75-100% of glomeruli.

20 Average scores for sclerotic change of individual specimens were calculated to quantify the degree of glomerular sclerosis. Average scores of glomerular sclerosis for individual specimens of rat groups administered with the drug were compared with those for control groups administered with the vehicle only to calculate glomerular sclerosis inhibition rates (%). The significance of differences was determined by the Dunnett method after testing homoscedasticity according to the Bartlett method.

25 Glomerular sclerosis inhibition rates (%) for the compound number 32 are shown as follows:

	Dose	Glomerular sclerosis inhibition rate (%)	Significance of difference
	10 mg/kg	11.7	p<0.05
	30 mg/kg	10.2	p<0.05
35	100 mg/kg	13.7	p<0.01

30 From the results above, it was shown that the compound number 32 has an effect in inhibiting pathological sclerotic changes of glomeruli in nephrosis associated with mesangial cell growth.

Test Example 3Antitumor activity45 1. Antitumor effect of the compound number 43 against mouse leukemia cells (P388)

40 The compound number 43 exhibited the following effect on prolonging survival of mice injected with tumor cells. P388 cells (1×10^6 cells), mouse leukemia cells obtained from ATCC, were inoculated intraperitoneally into CDF₁ mice (obtained from Japan SLC, Inc.), and then the test compound was administered intraperitoneally for 9 consecutive days at the dose of 100 mg/kg. The drug-treated animals survived longer than control animals by 130%.

50 2. Antitumor effect of the compound number 43 against human glioma cells (GL07)

The compound number 43 exhibited an antitumor effect in the nude mice human tumor xenograft model, a model which reflects clinical effect, as follows.

55 Human glioma, GL07 (obtained from the Central Institute for Experimental Animals), was transplanted into nude mice. When the tumor had grown to a volume of about 100 mm³, the nude mice were divided into several groups of 4 animals so as to equalize the average tumor volumes of each group. The test drug was administered orally to animals

in experimental groups 2 times a day for 14 consecutive days at 100 mg/kg, and the vehicle was administered to control animals. The tumor growth inhibition rate (TGIR, %) was calculated from the equation: $TGIR = (1-Tx/Cx) \times 100$, in which Cx is the tumor volume in the control mice and Tx is the tumor volume in the drug-treated mice, on day X, when the initial tumor volume at the time treatment was commenced is set 1. During the test period of about 4 weeks, the maximum TGIR value was 76%, and thus an excellent antitumor effect was observed.

5 From the results above, the compound number 43 was revealed to have an antitumor activity.

3. Antitumor effect of the compounds of the present invention against human glioma (GL07)

10 Each compounds exhibited an antitumor effect in the nude mice human tumor xenograft model, a model which reflects clinical effect, as follows.

15 Analogously to 2, human glioma cells, GL07 (obtained from the Central Institute for Experimental Animals), was transplanted into nude mice. When the tumor had grown to a volume of about 100 mm³, the nude mice were divided into several groups of 4 animals so as to equalize the average tumor volumes of each group. The test drug was administered orally to animals in experimental groups once a day for 9 consecutive days at 50 mg/kg, and the vehicle was administered to control animals. The tumor growth inhibition rate (TGIR, %) was calculated from the equation: $TGIR = (1-Tx/Cx) \times 100$, in which Cx is the tumor volume in the control mice and Tx is the tumor volume in the drug-treated mice, on day X, when the initial tumor volume at the time treatment was commenced is set 1. Results are shown in Table 3.

20

TABLE 3

	Compound No.	Tumor growth inhibition rate (TGIR, %)
25	(44)	78
	(45)	68
	(52)	86
30	(56)	52
	(57)	64
	(58)	57
35	(59)	82
	(165)	70
	(168)	56
	(173)	54
40	(190)	50
	(191)	50
	(194)	59
45	(225)	58
	(227)	78
	(229)	81
50	(235)	78
	(236)	84
	(237)	74
	(242)	62
55	(244)	73
	(254)	85
	(255)	86

TABLE 3 (continued)

Compound No.	Tumor growth inhibition rate (TGIR, %)
(260)	52
(262)	87
(264)	63
(267)	65
(272)	84

4. Antitumor effect of compounds numbers 43 and 58 against various tumor cells

15 In the same manner as described in 2, various types of tumor cells (obtained from the Central Institute for Experimental Animals) were transplanted into nude mice. When the tumor had grown to a volume of about 100 mm³, the animals were allocated to several groups each consisting of 4 animals so as to equalize the average tumor volume of each group. Test drugs were administered intraperitoneally to animals in experimental groups once a day for 9 consecutive days at 100 mg/kg, and the vehicle was administered to control animals. The resulting tumor growth inhibition rates 20 (TGIR) are shown in Table 4.

TABLE 4

Cells	Tumors	Tumor growth inhibition rate (TGIR, %)	
		(43)	(58)
COL-1	colon	68	74
St-4	stomach	78	86
L-27	lung	83	96

35 The results above revealed that the compounds of the present invention had antitumor effect on various types of tumors.

Test Example 4Effect on collagen-induced arthritis in mice

40 9-10 male DBA/1JNCrj mice (9 weeks old, purchased from Charles River Japan, Inc.) were used. An emulsion consisting of 5 ml of 0.3% bovine collagen type II (K-41, Collagen Gijyutsu-kenshukai, Japan), 15 mg of *Mycobacterium tuberculosis* H37Ra (obtained from Difco Labs.), 2.5 ml of physiological saline and 7.5 ml of Freund's incomplete adjuvant (Difco Labs.) was prepared, and then injected subcutaneously at the base of the tail (0.1 ml/animal) 2 times at 3 45 week intervals to induce arthritis. A test drug suspended in a vehicle, physiological saline containing 10% each of cremophor and DMSO, was administered intraperitoneally for 16 consecutive days, beginning one day before the second injection of the emulsion. Swelling of four legs, characteristic of the onset of arthritis, was investigated every day.

Effect of the compound number 43 on the incidence (%) of collagen-induced arthritis is shown as follows:

50

Dose	Number of mice with arthritis/total mice	Incidence (%)
Vehicle only	7/10	70
10 mg/kg	1/9	11
100 mg/kg	0/10	0

The results shown above revealed that the compound number 43 suppressed the incidence of collagen-induced arthritis.

Possible Industrial Use

5

Since the compounds of the present invention have inhibitory activity on abnormal cell growth, more specifically PDGF receptor autophosphorylation inhibitory activity, they are useful for treating numerous diseases such as leukemia, cancers, psoriasis, glomerulonephritis, organofibrosis, atherosclerosis, restenosis after percutaneous coronary angioplasty or bypass surgery and articular rheumatism. Therefore, the compounds can benefit greatly in treating humans and other animals which need these treatments.

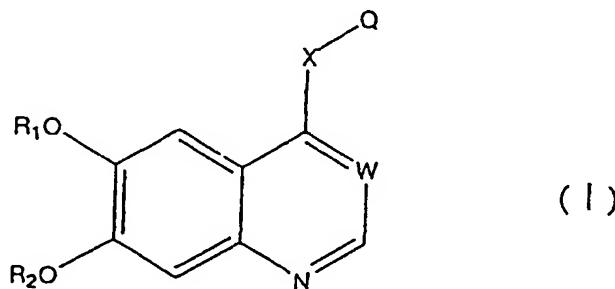
Claims

1. Quinoline derivatives and quinazoline derivatives represented by the following formula (I):

15

20

25



30

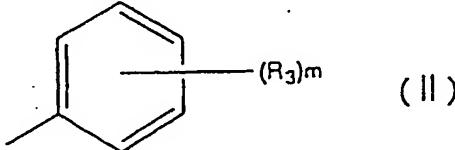
{wherein R₁ and R₂ are each independently H, C₁-C₅-alkyl, or R₁ and R₂ together form C₁-C₃-alkylene, and W is CH or N,

(1) when W is CH,

35

(a) X is O or S, and Q is a phenyl group represented by formula (II):

40

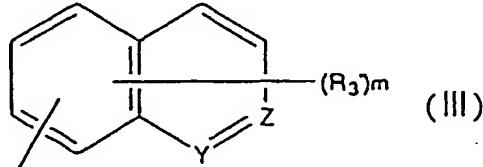


45

[wherein m is 1, 2 or 3, R₃ is each independently CN, OH, halogen, C₁-C₅-alkyl, C₁-C₄-alkoxy or C₂-C₄-acyl],

a group represented by formula (III):

50

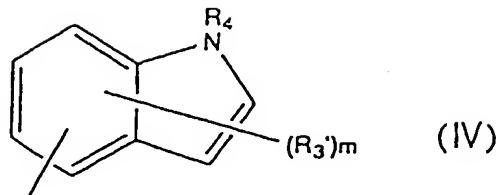


55

[wherein m is as defined as described above, R₃' is each independently OH, C₁-C₅-alkyl, C₁-C₄-alkoxy, and Y and Z are both or each independently N or CH],

or a group represented by formula (IV):

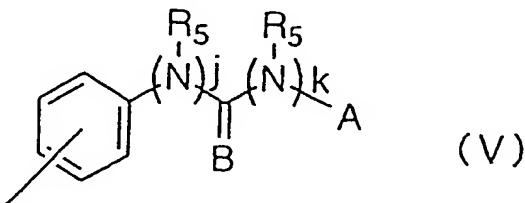
5



10

[wherein m and R₃ are as defined as described above, and R₄ is H, C₁-C₅-alkyl or C₂-C₄-acyl], and
(b) X is O, S or CH₂, and Q is a group represented by formula (V):

15



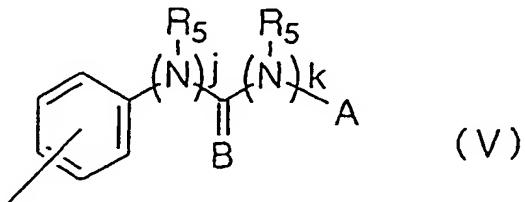
20

[wherein j and k are each independently 0 or 1, R₅ is each independently H or C₁-C₄-alkyl, A is C₁-C₈-alkyl, C₁-C₅-alkenyl, cyclic (C₃-C₁₀) alkyl, C₁-C₄-alkoxycarbonyl, phenyl, naphthyl, furyl, thiienyl, benzoyl, substituted benzoyl, C₂-C₄-acyl, or 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaryl group having 1 or 2 nitrogen atoms and optionally having another hetero atom selected from the group consisting of nitrogen, oxygen and sulfur atoms, these alkyl group, aryl group and heteroaryl group represented by A may have 1 to 5 substituents selected from the group consisting of CN, NO₂, OH, NH₂, halogen, C₁-C₅-alkyl, cyclic (C₃-C₁₀) alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxycarbonyl, C₁-C₅-acyl, C₁-C₅-acyloxy, C₁-C₃-alkylenedioxy, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, CO₂H, CONH₂, N-(C₁-C₄-alkyl)amido, N,N-di-(C₁-C₄-alkyl)amido, C₂-C₄-alkylamido, trifluoromethyl, C₁-C₄-alkylthio, phenyl, substituted phenyl, phenoxy, substituted phenoxy, phenylthio, substituted phenylthio, phenyl(C₁-C₄-alkyl), substituted phenyl(C₁-C₄-alkyl), pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopyperazinyl, morpholinyl, quinolyl, quinazolinyl, benzoyl, substituted benzoyl and C₂-C₄-acyl, and B is O, S, NH, NCN, NR₆ or NOR₆ (wherein R₆ is C₁-C₅-alkyl)].

35

(2) when W is N, X is O, S or CH₂, and Q is represented by formula (V):

40



45

[wherein j, k, R₅, A and B are defined as described above]] and pharmaceutically acceptable salts thereof.

50 2. Quinoline derivatives and pharmaceutically acceptable salts thereof according to Claim 1, characterized in that in formula (I), W is CH, X is O or S, and Q is formula (II), formula (III) or formula (IV).

3. Quinoline derivatives and pharmaceutically acceptable salts thereof according to Claim 1, characterized in that in formula (I), W is CH, X is O, and Q is formula (II), formula (III) or formula (IV).

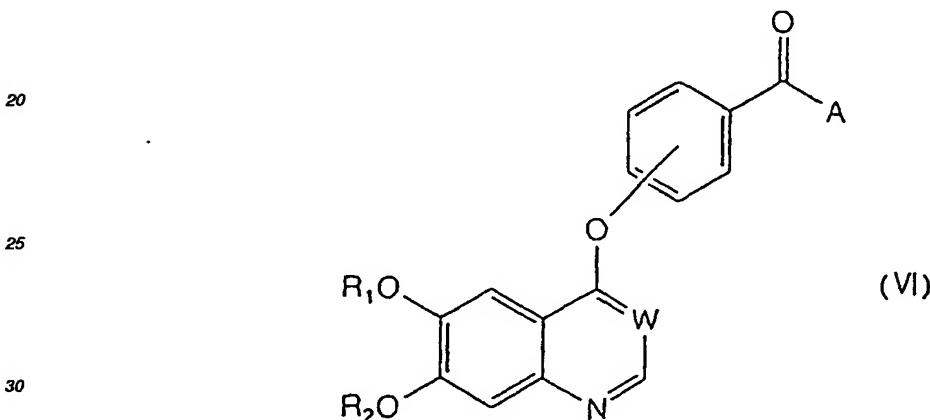
55 4. Quinoline derivatives and quinazoline derivatives and pharmaceutically acceptable salts thereof according to Claim 1, characterized in that in formula (I), X is O, S or CH₂, and Q is formula (V).

5. Quinoline derivatives and quinazoline derivatives and pharmaceutically acceptable salts thereof according to Claim 1, characterized in that in formula (I), R₁ and R₂ are each independently C₁-C₅-alkyl and Q is formula (V) [in formula (V), j and k are 0, B is O, S, NOR₆ (wherein R₆ is C₁-C₅-alkyl)].

5 6. Quinoline derivatives and quinazoline derivatives and pharmaceutically acceptable salts thereof according to Claim 1, characterized in that in formula (I), R₁ and R₂ are each independently C₁-C₅-alkyl and Q is formula (V) [in formula (V), j is 0 and k is 1, or j is 1 and k is 0, R₅ is hydrogen or methyl, B is O, S, NH, NCN, NR₆ or NOR₆ (wherein R₆ is C₁-C₅-alkyl)].

10 7. Quinoline derivatives and quinazoline derivatives and pharmaceutically acceptable salts thereof according to Claim 1, characterized in that in formula (I), R₁ and R₂ are each independently C₁-C₅-alkyl and Q is formula (V) [in formula (V), both j and k are 1, R₅ is each independently hydrogen or methyl, B is O, S, NH, NCN, NR₆ or NOR₆ (wherein R₆ is C₁-C₅-alkyl)].

15 8. Quinoline derivatives and quinazoline derivatives of formula (VI)



35 [wherein W is CH or N, R₁ and R₂ are each independently C₁-C₅-alkyl, A is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, isopentyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, naphthyl, furyl, thiienyl, pyridyl or pyrimidinyl, and these alkyl group, aryl group or heteroaryl group represented by A may have 1-5 substituents selected from the group consisting of fluoro, chloro, bromo, iodo, cyano, hydroxy, nitro, amino, methylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, trifluoromethyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, methoxy, ethoxy, propoxy, isopropoxy, morpholino, pyrrolidino, piperidino and butoxy] and pharmaceutically acceptable salts thereof.

40 9. Quinoline derivatives and quinazoline derivatives formula (VII)

45

50

55

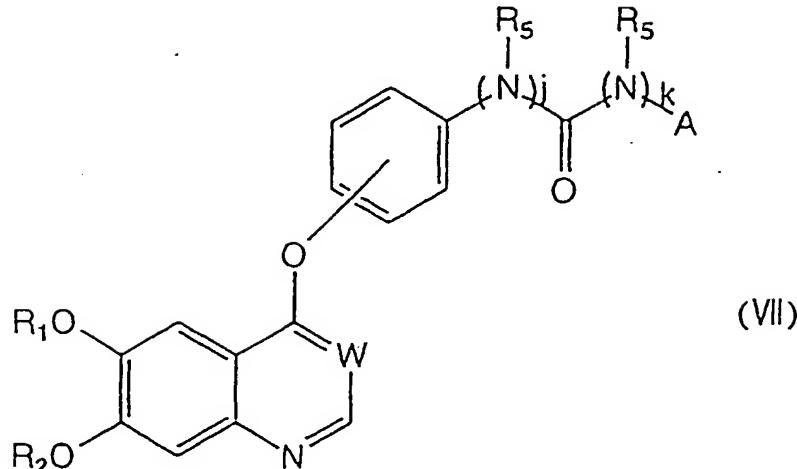
5

10

15

20

25



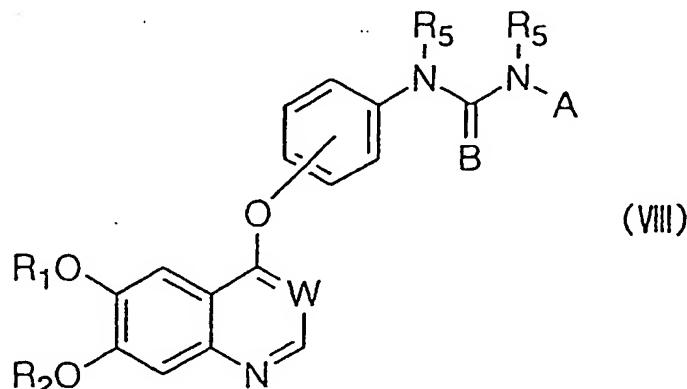
10. Quinoline derivatives and quinazoline derivatives of formula (VIII)

30

35

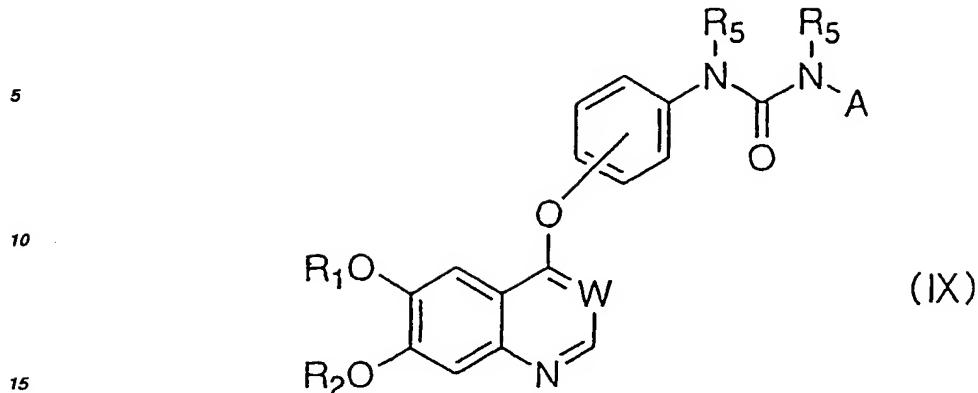
40

45



[wherein W is CH or N, R₁ and R₂ are each independently C₁-C₅-alkyl, R₅ is each independently hydrogen or methyl, A is C₁-C₆-alkyl, C₁-C₄-alkenyl, cyclopentyl, cyclohexyl, cycloheptyl, C₁-C₄-alkoxycarbonyl, phenyl, naphthyl, furyl, thieryl, benzoyl, acetyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl or morpholino, these alkyl group, aryl group or heteroaryl group represented by A may have 1-5 substituents selected from the group consisting of halogen, cyano, CO₂H, CONH₂, hydroxy, nitro, amino, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, C₁-C₅-acyloxy, C₁-C₅-acyl, C₁-C₄-alkylthio, trifluoromethyl, C₁-C₅-alkyl, C₁-C₄-alkoxyl, C₁-C₄-alkoxycarbonyl, N-(C₁-C₄-alkyl)amido, N,N-di-(C₁-C₄-alkyl)amido, C₂-C₄-alkylamido, ethylenedioxy, phenyl, phenoxy, substituted phenyl, benzoyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolyl and quinazolinyl, and B is O, S, NH, NCN, NR₆ or NOR₆ (in which R₆ is methyl) and pharmaceutically acceptable salts thereof.]

11. Quinoline derivatives and quinazoline derivatives of formula (IX)



[wherein W is CH or N, R₁ and R₂ are each independently C₁-C₅-alkyl, R₅ is each independently hydrogen or methyl, A is C₁-C₆-alkyl, C₁-C₄-alkenyl, cyclopentyl, cyclohexyl, cycloheptyl, C₁-C₄-alkoxycarbonyl, phenyl, naphthyl, furyl, thienyl, benzoyl, acetyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl or morpholino, and these alkyl group, aryl group or heteroaryl group represented by A may have 1-5 substituents selected from the group consisting of halogen, cyano, CO₂H, CONH₂, hydroxy, nitro, amino, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, C₁-C₅-acyloxy, C₁-C₅-acyl, C₁-C₄-alkylthio, trifluoromethyl, C₁-C₅-alkyl, C₁-C₄-alkoxyl, C₁-C₄-alkoxycarbonyl, N-(C₁-C₄-alkyl)amido, N,N-di-(C₁-C₄-alkyl)amido, C₂-C₄-alkylamido, ethylenedioxy, phenyl, phenoxy, substituted phenyl, benzoyl, pyridyl, pyrazinyl, pyrimidinyl pyridazinyl, quinolyl and quinazolinyl] and pharmaceutically acceptable salts thereof.

20

25

30

35

40

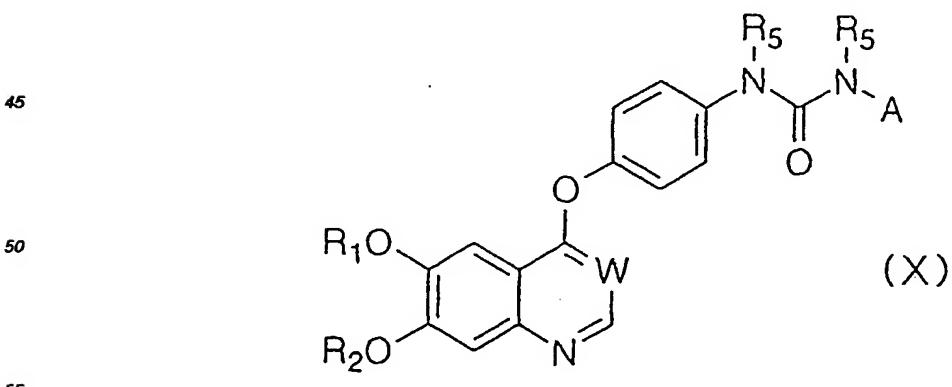
12. Quinoline derivatives and pharmaceutically acceptable salts thereof according to Claim 8, characterized in that in formula (VI), W is CH.

13. Quinoline derivatives and pharmaceutically acceptable salts thereof according to Claim 9, characterized in that in formula (VII), W is CH.

14. Quinoline derivatives and pharmaceutically acceptable salts thereof according to Claim 10, characterized in that in formula (VIII), W is CH.

15. Quinoline derivatives and pharmaceutically acceptable salts thereof according to Claim 11, characterized in that in formula (IX), W is CH.

16. Quinoline derivatives and quinazoline derivatives of formula (X)



[wherein W is CH or N, R₁ and R₂ are each independently C₁-C₅-alkyl, R₅ is each independently hydrogen or methyl, A is C₁-C₅-alkyl, cyclopentyl, cyclohexyl, cycloheptyl, allyl, C₁-C₄-alkoxycarbonyl, phenyl, naphthyl or ben-

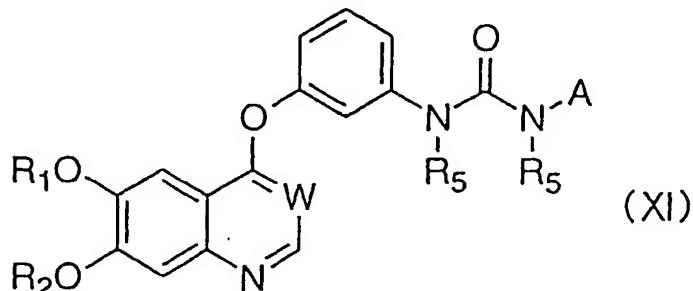
zoyl, and these alkyl group or aryl group represented by A may have 1-5 substituents selected from the group consisting of OH, CO₂H, fluoro, chloro, bromo, iodo, nitro, amino, di-(C₁-C₄-alkyl)amino, ethylenedioxy, acetoxy, methythio, C₁-C₄-alkoxycarbonyl, trifluoromethyl, C₁-C₄-alkyl, pyridyl and phenyl] and pharmaceutically acceptable salts thereof.

5

17. Quinoline derivatives and quinazoline derivatives of formula (XI)

10

15



20

25

[wherein W is CH or N, R₁ and R₂ are each independently C₁-C₅-alkyl, R₅ is each independently hydrogen or methyl, A is C₁-C₅-alkyl, cyclopentyl, cyclohexyl, cycloheptyl, allyl, C₁-C₄-alkoxycarbonyl, phenyl, naphthyl or benzoyl, and these alkyl group or aryl group represented by A may have 1-5 substituents selected from the group consisting of OH, CO₂H, fluoro, chloro, bromo, iodo, nitro, amino, di-(C₁-C₄-alkyl)amino, ethylenedioxy, acetoxy, methythio, C₁-C₄-alkoxycarbonyl, trifluoromethyl, C₁-C₄-alkyl, C₁-C₄-alkoxy, pyridyl and phenyl], and pharmaceutically acceptable salts thereof.

30

18. Quinoline derivatives and quinazoline derivatives according to Claim 1, characterized in that in formula (I), W is CH, X is O, both R₁ and R₂ are methyl, Q is formula (V) [in formula (V), j and k are each independently 0 or 1, R₅ is hydrogen, A is C₁-C₅-alkyl, cyclopentyl, cyclohexyl, cycloheptyl, allyl, C₁-C₄-alkoxycarbonyl, phenyl, naphthyl or benzoyl, these alkyl group, aryl group or heteroaryl group represented by A may have 1-5 substituents selected from the group consisting of OH, CO₂H, fluoro, chloro, bromo, iodo, nitro, amino, di-(C₁-C₄-alkyl)amino, ethylenedioxy, acetoxy, methythio, C₁-C₄-alkoxycarbonyl, trifluoromethyl, C₁-C₄-alkyl, C₁-C₄-alkoxy, pyridyl and phenyl, and B is O, S, NH, NCN, NR₆ or NOR₆ (in which R₆ is methyl)] and pharmaceutically acceptable salts thereof.

35

19. Compounds according to Claim 16, characterized in that in formula (I), W is CH, both R₁ and R₂ are methyl, and each R₅ is hydrogen, and pharmaceutically acceptable salts thereof.

40

45

20. Compounds of formula (I) according to Claim 1 selected from 6,7-dimethoxy-4-(2-methoxyphenoxy)quinoline, 6,7-dimethoxy-4-(3-methoxyphenoxy)quinoline, 6,7-dimethoxy-4-(4-methoxyphenoxy)quinoline, 4-(3-fluorophenoxy)-6,7-dimethoxyquinoline, 4-(3-hydroxyphenoxy)-6,7-dimethoxyquinoline, 4-(4-bromophenoxy)-6,7-dimethoxyquinoline, 4-(3,4-dimethoxyphenoxy)-6,7-dimethoxyquinoline, 6,7-dimethoxy-4-(1-naphthylloxy)quinoline, 6,7-dimethoxy-4-(2-naphthylloxy)quinoline, 6,7-dimethoxy-4-(5-methoxy-1-naphthylloxy)quinoline, 6,7-dimethoxy-4-(6-methoxy-2-naphthylloxy)quinoline, 6,7-dimethoxy-4-(7-methoxy-2-naphthylloxy)quinoline, 6,7-dimethoxy-4-(5-quinolylloxy)quinoline, 6,7-dimethoxy-4-(6-quinolylloxy)quinoline, 4-(4-indolylloxy)-6,7-dimethoxyquinoline, 4-(5-indolylloxy)-6,7-dimethoxyquinoline, 6,7-dimethoxy-4-(3-methoxyphenylthio)quinoline and 6,7-dimethoxy-4-(4-methoxyphenylthio)quinoline, and pharmaceutically acceptable salts thereof.

50

55

21. Compounds of formula (I) according to Claim 1 selected from (4-n-butylphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone, (4-t-butylphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone, (4-trifluoromethylphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone, (4-t-butylphenyl){4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}methanone, (4-t-butylphenyl){4-[(6,7-dimethoxy-4-quinolyl)methyl]phenyl}methanone, N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-cyclohexanecarboxamide, N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}- (4-nitrophenyl)carboxamide, N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-(N,N-dimethylaminophenyl)carboxamide, N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-(4-acetylphenyl)carboxamide, N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-(4-n-butylphenyl)carboxamide, N-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-(4-butoxy-

5 phenyl)carboxamide, N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-(4-bromophenyl)carboxamide, N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]cyclopantanecarboxamide, N-(4-n-butylphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(4-t-butylphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(2-trifluoromethylphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(3-trifluoromethylphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(4-trifluoromethylphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(2-methoxyphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(3-methoxyphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(2-fluorophenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(3-fluorophenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(4-fluorophenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(4-acetylphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea, N-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)urea, N-(4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl)-N'-n-propylurea, N-n-butyl-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]phenylurea, N-(2-fluorophenyl)-N'-[4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]urea, N-(3-methoxyphenyl)-N'-[4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]urea, N-(4-methoxyphenyl)-N'-[4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]urea, N-n-butyl-N'-[4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]urea, {4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}[4-morpholinophenyl]methanone, {4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}[4-pyrrolidinophenyl]methanone, {4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}[4-piperidinophenyl]methanone, N-(2,4-dichlorophenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(3,4-dichlorophenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(4-chloro-2-methylphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(3-amino-4-chlorophenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N-(2-pyridylmethyl)urea, N-(3,4-difluorophenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, N-(2,4,5-trifluorophenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea and N-(4-hydroxyphenyl)-N'-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]urea, and pharmaceutically acceptable salts thereof.

25 22. A pharmaceutical composition which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and pharmaceutically acceptable salts thereof according to any one of Claims 1-21 having platelet-derived growth factor receptor autophosphorylation inhibitory activity.

30 23. A pharmaceutical composition for use in treating tumors, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 1-21.

35 24. A pharmaceutical composition for use in treating psoriasis, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 1-21.

40 25. A pharmaceutical composition for use in treating atherosclerosis, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 1-21.

45 26. A pharmaceutical composition for use in treating restenosis after percutaneous coronary angioplasty or bypass surgery, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 1-21.

50 27. A pharmaceutical composition for use in treating glomerulonephritis, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 1-21.

55 28. A pharmaceutical composition for use in treating organofibrosis, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 1-21.

29. A pharmaceutical composition for use in treating leukemia, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 1-21.

30. A pharmaceutical composition for use in treating articular rheumatism, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically accept-

able salts according to any one of Claims 1-21.

31. A pharmaceutical composition for use in treating glomerulonephritis, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to Claim 5, 8 or 12.
- 5 32. A pharmaceutical composition for use in treating tumors, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 7, 10, 11, 14, 15, 16, 17 and 19.
- 10 33. A pharmaceutical composition for use in treating leukemia, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 7, 10, 11, 14, 15, 16, 17 and 19.
- 15 34. A pharmaceutical composition for use in treating articular rheumatism, which comprises at least one compound, as an effective component, selected from the group consisting of the compounds and their pharmaceutically acceptable salts according to any one of Claims 7, 10, 11, 14, 15, 16, 17 and 19.
- 20 35. A method for treating neoplastic tumors, which comprises administering an effective amount of the compounds according to any one of Claims 1-21 to patients who need treatment for neoplastic tumors.
36. A method for treating psoriasis, which comprises administering an effective amount of the compounds according to any one of Claims 1-21 to patients who need treatment for psoriasis.
- 25 37. A method for treating atherosclerosis, which comprises administering an effective amount of the compounds according to any one of Claims 1-21 to patients who need treatment for atherosclerosis.
- 30 38. A method for treating restenosis after percutaneous coronary angioplasty or bypass surgery, which comprises administering an effective amount of the compounds according to any one of Claims 1-21 to patients who need treatment for restenosis after percutaneous coronary angioplasty or bypass surgery.
39. A method for treating glomerulonephritis, which comprises administering an effective amount of the compounds according to any one of Claims 1-21 to patients who need treatment for glomerulonephritis.
- 35 40. A method for treating organofibrosis, which comprises administering an effective amount of the compounds according to any one of Claims 1-21 to patients who need treatment for organofibrosis.
41. A method for treating leukemia, which comprises administering an effective amount of the compounds according to any one of Claims 1-21 to patients who need treatment for leukemia.
- 40 42. A method for treating articular rheumatism, which comprises administering an effective amount of the compounds according to any one of Claims 1-21 to patients who need treatment for articular rheumatism.
43. A method for treating glomerulonephritis, which comprises administering an effective amount of the compounds according to Claim 5, 8 or 12 to patients who need treatment for glomerulonephritis.
- 45 44. A method for treating tumors, which comprises administering an effective amount of the compounds according to any one of Claims 7, 10, 11, 14, 15, 16, 17 and 19 to patients who need treatment for tumors.
- 50 45. A method for treating leukemia, which comprises administering an effective amount of the compounds according to any one of Claims 7, 10, 11, 14, 15, 16, 17 and 19 to patients who need treatment for leukemia.
46. A method for treating articular rheumatism, which comprises administering an effective amount of the compounds according to any one of Claims 7, 10, 11, 14, 15, 16, 17 and 19 to patients who need treatment for articular rheumatism.
- 55 47. Use of the compounds according to any one of Claims 1 to 21 for manufacturing pharmaceutical compositions.

48. Use of the compounds according to any one of Claims 7, 10, 11, 14, 15, 16, 17 and 19 for manufacturing antitumor agents.

5 49. Use of the compounds according to any one of Claims 7, 10, 11, 14, 15, 16, 17 and 19 for manufacturing therapeutic agents for articular rheumatism.

10

15

20

25

30

35

40

45

50

55

INTERNATIONAL SEARCH REPORT		International application No. PCT/JP96/03229															
A. CLASSIFICATION OF SUBJECT MATTER Int. Cl ⁶ C07D215/20, 215/22, 215/36, 239/74, 239/88, 239/93, 401/12, 405/12, 409/12, 491/056, A61K31/47, 31/505 According to International Patent Classification (IPC) or to both national classification and IPC																	
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int. Cl ⁶ C07D215/20, 215/22, 215/36, 239/74, 239/88, 239/93, 401/12, 405/12, 409/12, 491/056, A61K31/47, 31/505																	
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched																	
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE																	
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; padding: 2px;">Category*</th> <th style="text-align: left; padding: 2px;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="text-align: left; padding: 2px;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; padding: 2px;">Y</td> <td style="padding: 2px;">JP, 6-507643, A (Rhone-Poulenc Rorer International (Holdings) Inc.), September 1, 1994 (01. 09. 94) & WO, 92/20642, A</td> <td style="text-align: center; padding: 2px;">1-34, 47-49</td> </tr> <tr> <td style="text-align: center; padding: 2px;">Y</td> <td style="padding: 2px;">US, 5480883, A (Rhone-Poulenc Rorer Pharmaceuticals Inc.), January 2, 1996 (02. 01. 96) (Family: none)</td> <td style="text-align: center; padding: 2px;">1-34, 47-49</td> </tr> <tr> <td style="text-align: center; padding: 2px;">Y</td> <td style="padding: 2px;">JP, 60-120872, A (Kyowa Hakko Kogyo Co., Ltd.), June 28, 1985 (28. 06. 85) (Family: none)</td> <td style="text-align: center; padding: 2px;">1-34, 47-49</td> </tr> <tr> <td style="text-align: center; padding: 2px;">Y</td> <td style="padding: 2px;">JP, 57-158780, A (Bristol-Myers Co.), September 30, 1982 (30. 09. 82) & US, 4343940, A & DE, 3203770, A</td> <td style="text-align: center; padding: 2px;">1-43, 47-49</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	JP, 6-507643, A (Rhone-Poulenc Rorer International (Holdings) Inc.), September 1, 1994 (01. 09. 94) & WO, 92/20642, A	1-34, 47-49	Y	US, 5480883, A (Rhone-Poulenc Rorer Pharmaceuticals Inc.), January 2, 1996 (02. 01. 96) (Family: none)	1-34, 47-49	Y	JP, 60-120872, A (Kyowa Hakko Kogyo Co., Ltd.), June 28, 1985 (28. 06. 85) (Family: none)	1-34, 47-49	Y	JP, 57-158780, A (Bristol-Myers Co.), September 30, 1982 (30. 09. 82) & US, 4343940, A & DE, 3203770, A	1-43, 47-49
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.															
Y	JP, 6-507643, A (Rhone-Poulenc Rorer International (Holdings) Inc.), September 1, 1994 (01. 09. 94) & WO, 92/20642, A	1-34, 47-49															
Y	US, 5480883, A (Rhone-Poulenc Rorer Pharmaceuticals Inc.), January 2, 1996 (02. 01. 96) (Family: none)	1-34, 47-49															
Y	JP, 60-120872, A (Kyowa Hakko Kogyo Co., Ltd.), June 28, 1985 (28. 06. 85) (Family: none)	1-34, 47-49															
Y	JP, 57-158780, A (Bristol-Myers Co.), September 30, 1982 (30. 09. 82) & US, 4343940, A & DE, 3203770, A	1-43, 47-49															
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																	
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed																	
Date of the actual completion of the international search January 10, 1997 (10. 01. 97)		Date of mailing of the international search report January 21, 1997 (21. 01. 97)															
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.		Authorized officer Telephone No.															

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP96/03229

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 35 - 46
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 35 to 46 pertain to methods for treatment of the human body by therapy.

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.